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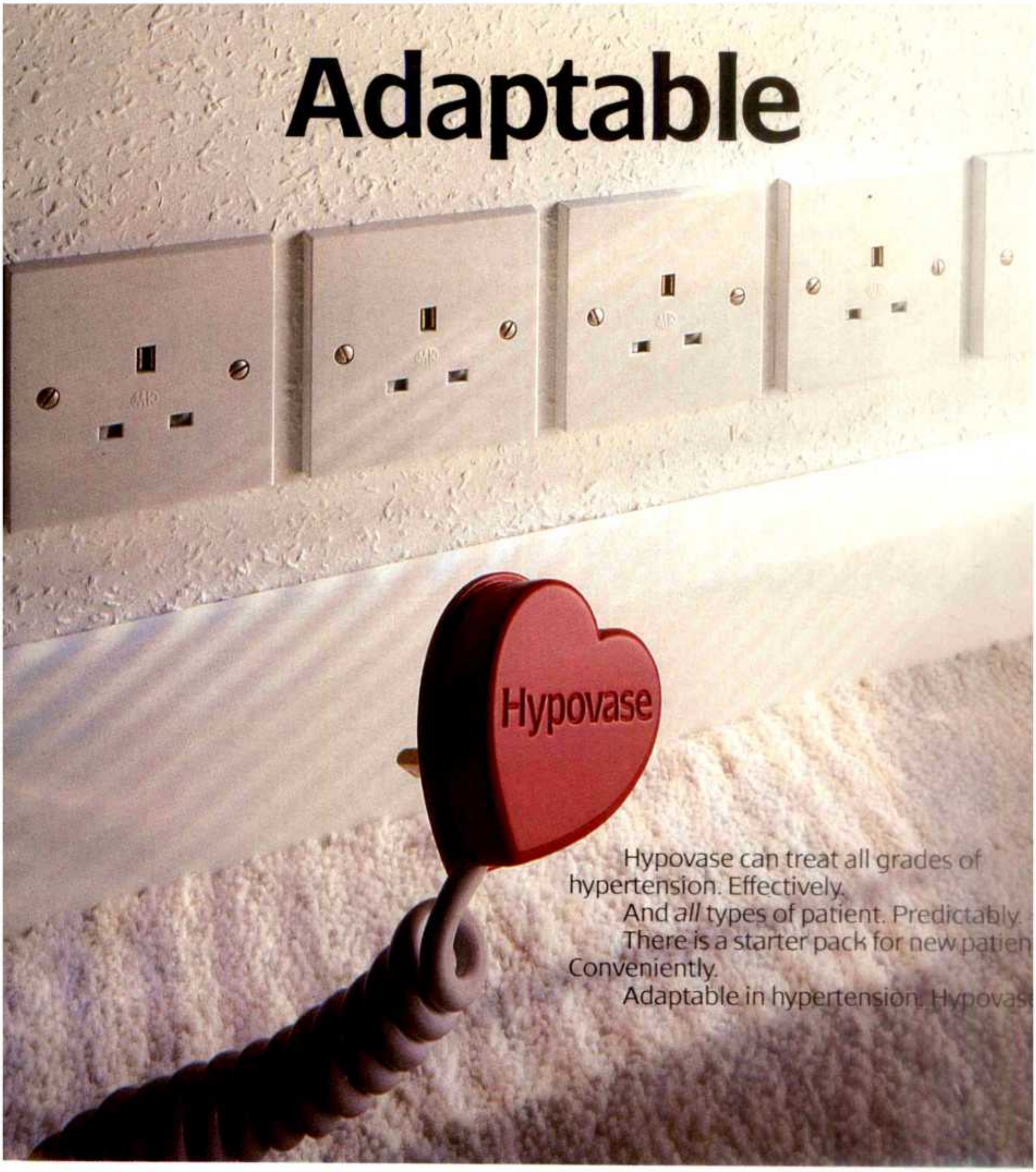

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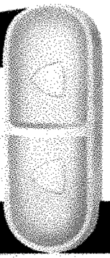
ABBREVIATED PRESCRIBING INFORMATION Presentation: 240 mg verapamil hydrochloride BP in a sustained release formulation. **Indications:** Mild to moderate hypertension. **Dose:** One tablet daily. For patients new to verapamil therapy doctors should consider an initial dose of 120 mg. Maximum dose two tablets daily in divided doses. **Elderly:** normal dosage unless hepatic or renal impairment. **Contra-indications:** Cardiogenic shock, acute myocardial infarction complicated by bradycardia, hypotension, left ventricular failure, second or third degree AV block, sick sinus syndrome, uncompensated heart failure, marked bradycardia, marked hypotension. **Precautions:** Use cautiously in patients with first degree AV block, atrial flutter/fibrillation with an accessory pathway, hepatic, renal disease, first trimester pregnancy. Left ventricular contractility may be affected and in a very few cases cardiac failure may be precipitated or aggravated. Use cautiously in patients receiving beta-blockers, digoxin, anti-arrhythmic agents, inhaled anaesthetics. The effects of Securon SR may be additive to other anti-hypertensive agents. **Side-effects:** Generally



1-A-DAY
FOR HYPERTENSIVES.

well tolerated. Constipation may occur, occasionally flushing, rarely headache, vomiting, nausea, dizziness, fatigue and ankle oedema, very rarely hypersensitivity reaction. **Product licence number:** 0169/0007. **Basic NHS price:** Securon SR calendar pack of 28 x 240mg tablets – £10.92, 100 x 240mg tablets – £39.00. Further information available from Knoll Ltd, The Brow, Burgess Hill, West Sussex RH15 9NE. Securon is a registered trademark of Knoll AG

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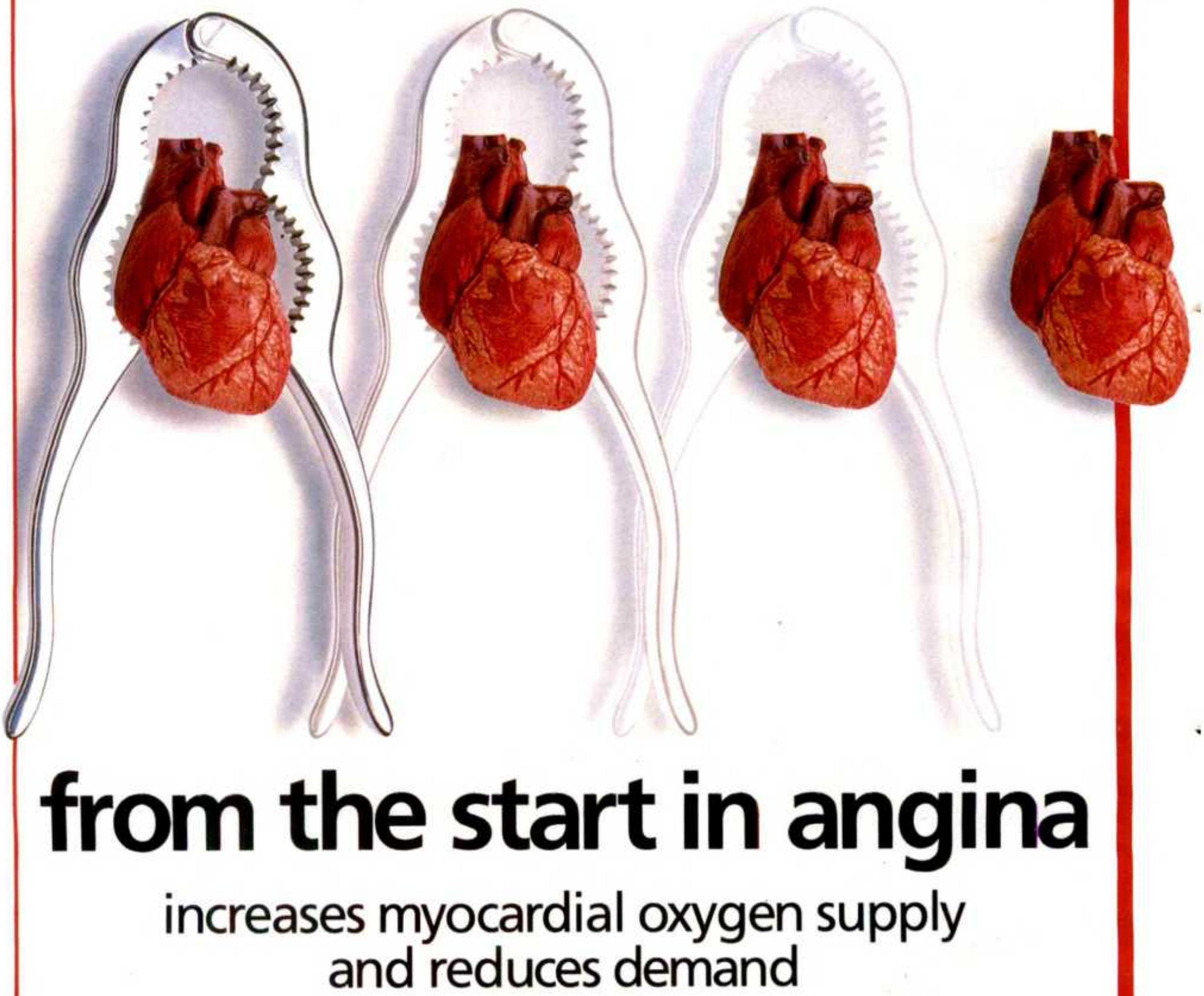

from the start in angina

increases myocardial oxygen supply
and reduces demand

Prescribing Information. Presentation: Adalat/Adalat 5: Orange, soft gelatine capsules containing a yellow viscous liquid. Adalat capsules are over-printed with 'ADALAT' and contain 10 mg nifedipine. Adalat 5 capsules contain 5 mg nifedipine. **Indications:** For the treatment and prophylaxis of angina pectoris. **Dosage and Administration:** For oral administration, the capsules should be taken with a little fluid during or after meals. The recommended dose is one 10 mg capsule three times daily. If necessary, up to two capsules three times daily may be taken. If an immediate effect is required, the capsule should be bitten open and the liquid contents allowed to remain in the mouth. Adalat 5 capsules permit titration of initial dosage in the elderly and those patients on concomitant medication. The recommended dose is one Adalat 5 capsule three times daily. **Contra-indications:** Must not be given to women capable of child bearing. **Warnings and Precautions:** Adalat is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days. Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adalat will not prevent possible rebound effects after cessation of antihypertensive therapy. Adalat should be used with caution in patients whose cardiac reserve is poor. Ischaemic pain has been reported in a small proportion of patients within 30 minutes of the introduction of Adalat therapy. Patients experiencing this effect should discontinue Adalat. The use of Adalat in diabetic patients may require adjustment of their control. The antihypertensive effect of nifedipine can be potentiated by simultaneous administration with cimetidine. When used in combination with nifedipine, serum quinidine levels have been shown to be suppressed regardless of dosage of quinidine. **Side Effects:** Adalat is well tolerated. Minor side-effects, usually associated with vasodilatation are mainly headache, flushing and lethargy. Gravitational oedema associated with increased capillary filtration capacity has been reported. These effects are transient and invariably disappear with continued treatment. **Over-dosage:** Standard measures such as atropine and noradrenaline may be used for resultant bradycardia and hypotension. Intravenous calcium gluconate may be of benefit combined with metaraminol. **Package Quantities:** Adalat and Adalat 5 are available in foil strips of 10 in packs of 100. **Daily Treatment Cost:** Adalat-37p per 3 capsules. Adalat 5-25p per 3 capsules. **Product Licence Numbers:** Adalat UK PL0010/0021. Adalat 5 UK PL0010/0079. Republic of Ireland: Adalat PA21/31. Adalat 5

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Br Heart J 1987;57:1

Editorial

Cardiac Club 1922: Cardiac Society of Great Britain and Ireland 1937

DENNIS KRIKLER

Editor, British Heart Journal

This year sees the Golden Jubilee of the transformation of the Cardiac Club into the Cardiac Society of Great Britain and Ireland, now known as the British Cardiac Society. The origins of both the Cardiac Club and the Cardiac Society were recounted in an article in the first issue of the *British Heart Journal* published in 1939,[1] which we reprint in this issue so that our readers can more easily appreciate the events. Fortunately we have been able to obtain from one of the founding fathers, indeed the first President of the Cardiac Society, a more personal account of the circumstances.[2] The invitation to Gilchrist produced a quick response, and the article was written in his elegant hand, clearly legible, and ready for the printer as it stood. It is gratifying to know that several of the founding fathers are with us and able to see with what pleasure we commemorate their vision in establishing the Society half a century ago.

The *British Heart Journal* is two years younger than the Cardiac Society, and as its official organ we are happy to publish a series of Jubilee editorials which will try to reflect a selected series of developments in cardiology that span the time of the establishment of the Society and that have continued to be important to this day. In selecting the topics and writers, it was gratifying to see what a fruitful period this has been for British cardiology. In addition to our usual papers, each subsequent issue will start with a Jubilee editorial written in this spirit. One subject of considerable importance, to which the British contribution has been substantial, has been omitted and that is cardiac surgery; having read the recent review by Cleland, we realised how difficult it would be for anyone else to cover the subject without trespassing on his achievement.[3]

References

1 Cowan J and others. Some notes on the Cardiac Club. *Br Heart J* 1939;1.97–104 (see also this issue, pages 3–10).

2 Gilchrist R. British Cardiac Society — Golden Jubilee. *Br Heart J* 1987;57.2

3 Cleland WP. The evolution of cardiac surgery in the United Kingdom. *Thorax* 1983;38.887–96

Br Heart J 1987;57:2

Jubilee Editorial

British Cardiac Society—Golden Jubilee

RAE GILCHRIST

Consulting physician, Royal Infirmary, Edinburgh

The British Cardiac Society had its origin in the Cardiac Club which consisted of 15 members bound together by their interest in cardiology. The Club held its first meeting in London in 1922 under the chairmanship of Sir Thomas Lewis and annually thereafter, with one or two new members added most years. As a source of lasting friendship, understanding, and good fellowship it made an indelible impression on its fortunate members. First and foremost, they were firm friends, united in a common interest in cardiology. I was astounded by the warmth of the welcome that I received on my admission to the club, only two members of which I had met previously. I felt I was among old friends.

At the Club's dinner after the annual meeting held in London in 1935, under the chairmanship of Sir Maurice Cassidy, I put forward the suggestion that the Club should expand, extend its benefits to a wider group, and act as a forum for the presentation of clinical research and discussion. I said we needed a British Cardiac Society with its own journal. Without any preliminary soundings before dinner, this proposal transformed the evening. It was seconded by Evan Bedford and received with enthusiasm with only one dissenter — Maurice Campbell — who subsequently changed his mind and a few years later became secretary of the new Society, soon to become the passion of his life! A constitution was drawn up and invitations were sent to 50 possible new members — all hand-picked; all accepted, and we were off to a good start.

We held our first annual meeting at the Royal Infirmary in Edinburgh in 1937 and I was Chairman that year. Among several communications that of Paul Wood was outstanding; he made a deep impression. The Society dined in the Hall of the Royal College of Physicians of Edinburgh. It was a memorable occasion, a dozen or more members accepting my invitation to continue the celebration of the successful birth of a new Society at my home, then within walking distance of the College. The Association of Physicians met the following day, dined in the same Hall, and only a few noticed that the caterers provided identical menus on successive nights.

In the early days it was an honour to be selected for membership of the Cardiac Club and of the British Cardiac Society as a foundation member. Now it is commonplace, but much appreciated by the younger members who value the opportunity to see, hear, and meet many of the leading cardiologists of the day, but perhaps on occasions a two-headed sword, as exemplified by a younger member telling me that having seen and heard a certain elder "statesman" take part in a discussion he (the younger) would never bother to read anything he (the elder) wrote in the future.

At one time all the members were known to each other. Those days have passed and now an enormous audience of members and guests gathers in one of two or three halls for simultaneous presentation of different communications, discussions, or lectures according to personal choice. The Society now consists of close on 800 members, of whom 200 or more reside abroad. It was in 1952, the year when the European Cardiological Congress was held in London, that Sir John Parkinson was elected our President. Similarly, in 1970 Sir John McMichael was President during the meeting of the World Congress of Cardiology in London. Professor Michael Oliver, the Society's eighth President and the first to be elected from outside London, brought Edinburgh an additional distinction.

The Society is responsible for two major publications — the *British Heart Journal* and *Cardiovascular Research*—both distributed world wide to subscribers and making an enormous contribution to cardiology. The *British Heart Journal* was originally intended for British contributors, thereby reflecting the British outlook, approach, and attitude to widening knowledge, but it now includes papers from all over the world, recognition of its standing abroad.

In brief, the Society has attained a stature and a success greater than ever expected. Nevertheless, "small is beautiful" and the Cardiac Club in its personal relationships had its own particular charm, denied to the larger, more efficient, but impersonal organisation of the present day.

Br Heart J 1987;57:3–10

SOME NOTES ON THE CARDIAC CLUB

BY

JOHN COWAN AND OTHERS

> *"The Sun of our body, the King and sole Commander of it"*—
> *"Anatomy of Melancholy"*

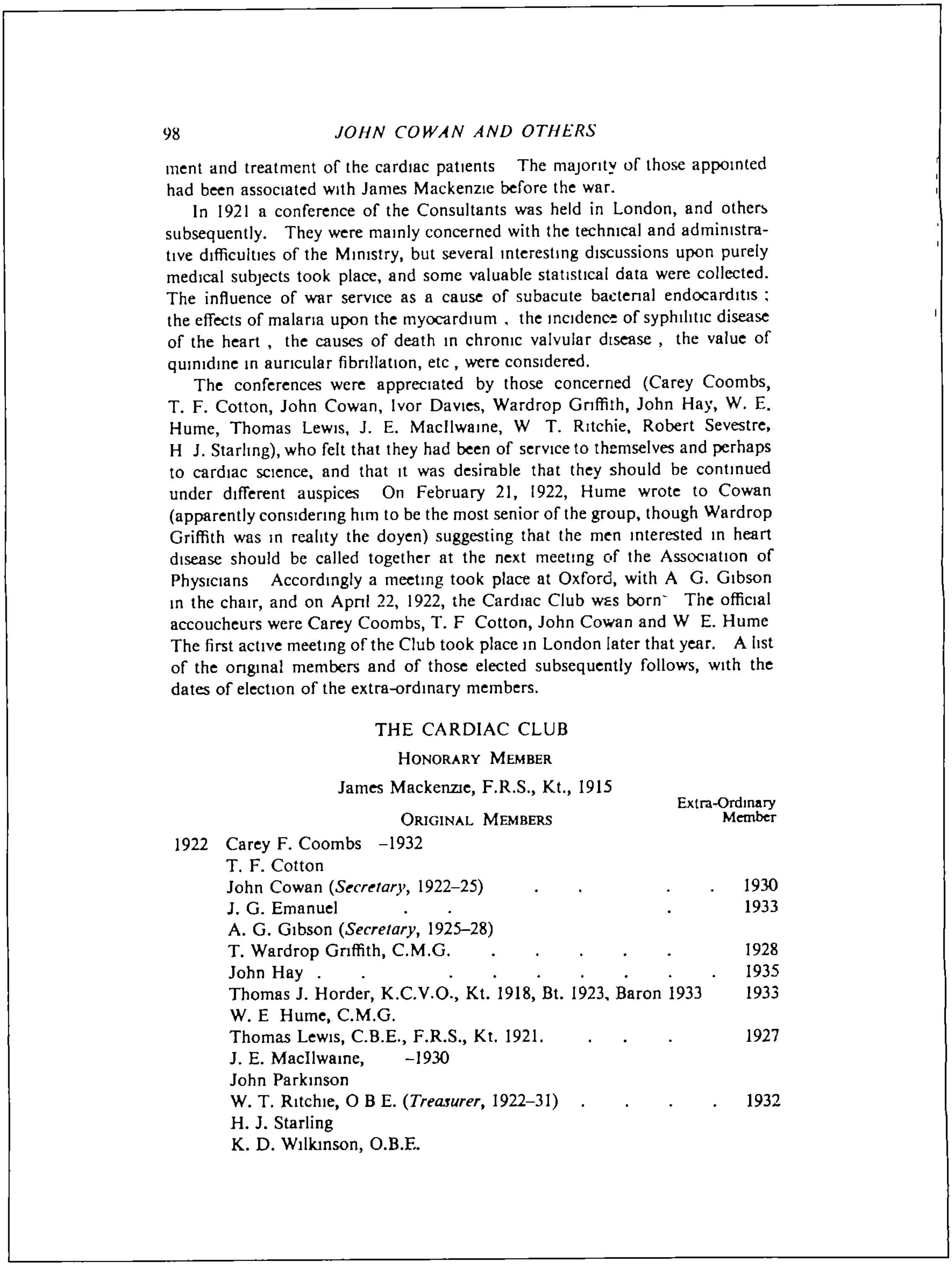
It is difficult to convey to the Georgian a proper impression of the attitude of the late Victorians to heart disease. Laennec's discovery of auscultation dominated the succeeding fifty years, and towards the end of the century the characteristic sounds of the various valvular lesions had been fully elucidated. For a time medicine stagnated. Those of us who were Residents in medical wards viewed the outlook with dismay, for the progress of surgery at that time, under the influence of Lister's work, was phenomenal. But better times were at hand.

The physiological laboratories were at work under Gaskell and others. The bacteriologists were turning their attention to medical subjects, the tubercle bacillus was discovered by Koch. X-rays showed the contents of the thorax. The sphygmomanometer was adapted for clinical use, and the polygraph and later the electrocardiograph added their quota to the general store.

But, although new methods of investigation became available, a personal influence was needed to speed up the work, and James Mackenzie became the centre of the picture. He had many facets. A tall, burly man, with all the directness of the North, he seemed at first sight rather dictatorial and overbearing; but his transparent goodwill, his unselfishness, and his humility soon made manifest that it was merely his intolerance of sham, and his search for truth. His intensive study of the Shorter Catechism had inculcated a downright mode of expression! He took a kindly interest in all his neighbours, especially the younger members of his profession; and he was always receptive of opinions based upon material which was outwith his own opportunities. Before long he had attracted to himself many men who were interested in the problems of heart disease, and had himself suggested to some of our members that a small club should be formed for meetings and discussions The Cardiac Club was conceived in Burnley.

Another European war came, and our profession was scattered over the world. It was not a great war, for it altered little save garden fences, but it left a terrible swathe behind it. Many men had died, and many more were suffering in health, from wounds or sickness, for whom provision was required During the war the Pension Service was necessarily a makeshift; the staff was insufficient and inexperienced, and their decisions needed revision and co-ordination. Many of the cases were cardiac, at least in name, so, in April 1920, the Ministry appointed Consultants to aid the Regional Directors in the assess-

(British Heart Journal, Vol. 1, No. 1, January, 1939)



ment and treatment of the cardiac patients The majority of those appointed had been associated with James Mackenzie before the war.

In 1921 a conference of the Consultants was held in London, and others subsequently. They were mainly concerned with the technical and administrative difficulties of the Ministry, but several interesting discussions upon purely medical subjects took place, and some valuable statistical data were collected. The influence of war service as a cause of subacute bacterial endocarditis ; the effects of malaria upon the myocardium , the incidence of syphilitic disease of the heart , the causes of death in chronic valvular disease , the value of quinidine in auricular fibrillation, etc , were considered.

The conferences were appreciated by those concerned (Carey Coombs, T. F. Cotton, John Cowan, Ivor Davies, Wardrop Griffith, John Hay, W. E. Hume, Thomas Lewis, J. E. MacIlwaine, W T. Ritchie, Robert Sevestre, H J. Starling), who felt that they had been of service to themselves and perhaps to cardiac science, and that it was desirable that they should be continued under different auspices On February 21, 1922, Hume wrote to Cowan (apparently considering him to be the most senior of the group, though Wardrop Griffith was in reality the doyen) suggesting that the men interested in heart disease should be called together at the next meeting of the Association of Physicians Accordingly a meeting took place at Oxford, with A G. Gibson in the chair, and on April 22, 1922, the Cardiac Club was born The official accoucheurs were Carey Coombs, T. F Cotton, John Cowan and W E. Hume The first active meeting of the Club took place in London later that year. A list of the original members and of those elected subsequently follows, with the dates of election of the extra-ordinary members.

THE CARDIAC CLUB

HONORARY MEMBER

James Mackenzie, F.R.S., Kt., 1915

ORIGINAL MEMBERS

		Extra-Ordinary Member
1922	Carey F. Coombs -1932	
	T. F. Cotton	
	John Cowan (*Secretary*, 1922–25)	1930
	J. G. Emanuel	1933
	A. G. Gibson (*Secretary*, 1925–28)	
	T. Wardrop Griffith, C.M.G.	1928
	John Hay	1935
	Thomas J. Horder, K.C.V.O., Kt. 1918, Bt. 1923, Baron 1933	1933
	W. E Hume, C.M.G.	
	Thomas Lewis, C.B.E., F.R.S., Kt. 1921.	1927
	J. E. MacIlwaine, -1930	
	John Parkinson	
	W. T. Ritchie, O B E. (*Treasurer*, 1922–31)	1932
	H. J. Starling	
	K. D. Wilkinson, O.B.E.	

(British Heart Journal, Vol. 1, No. 1, January, 1939)

THE CARDIAC CLUB—*continued*

Members Elected Subsequently

1923	J. Crighton Bramwell (*Secretary*, 1928–32)
	Francis R. Fraser
1924	A. N. Drury, F.R.S.
	C. E. K. Herapath, M.C.
1925	A. M. Kennedy
	S. Wentworth Patterson
1926	George A. Allan
	Maurice A. Cassidy, C.B., K.C.V.O., Kt. 1934
1927	S. B. Boyd Campbell, M.C
	Arnold W. Stott
1928	H. Wallace Jones
	D. Evan Bedford (*Secretary*, 1932–36)
1930	E. P. Poulton
1931	J. Maurice Campbell, O.B.E. (*Secretary*, 1936–37)
1933	R. T. Grant, F.R.S.
	A. R. Gilchrist
1934	Leonard Abrahamson
	C. W. Curtis Bain, M.C.
1936	C. Bruce Perry

Of these original members, three have died: Carey Coombs in his full vigour in 1932, MacIlwaine of Belfast in 1930, and James Mackenzie in 1925. At their next meeting the Club put on record this expression of appreciation of their only Honorary Member; and short notes of the dates and appointments of these three members follow.

Minute of the Cardiac Club, May 28, 1925

" The Cardiac Club laments the death, on January 26, 1925, of its Honorary Member, Sir James Mackenzie. By the power of his genius and the wealth of his achievements he exercised a vast influence upon the branch of Medicine with which his name is indissolubly associated ; and his pre-eminence, transcending the limitations of race and clime, was universally acknowledged. So long as the Science of Medicine endures so long will the name of Sir James Mackenzie be honoured.

" This tribute is rendered to the memory of him whom all Members of the Cardiac Club revered as their Master , and the Club respectfully offers its sincere sympathy to Lady Mackenzie and Miss Mackenzie in the great loss which they have sustained."

James Mackenzie, 1853–1925

M.B., 1878 ; M D., 1882 , F.R.C P., London, 1913. F.R.S , 1915. LL.D., Aberdeen, 1910 ; Edinburgh, 1911. Knight, 1915. Hon. Physician to H.M. the King in Scotland, 1920

Physician, Victoria Hospital, Burnley ; 1880–1907. Physician, Mount Vernon Hospital for Diseases of the Chest , 1910–18. Physician to the Cardiac Department, London Hospital, 1911–18. Director of the St. Andrew's Institute of Clinical Research, 1918–25. Schorstein Lecturer, 1911. Oliver Sharpey Lecturer, 1911. George A. Gibson Lecturer, 1914.

Carey Franklin Coombs, 1879–1932

M.B., 1901. M.D., 1903. F.R.C.P., 1917.

Physician, Bristol General Hospital, 1920. Director, Bristol University Centre of Cardiac Research, 1927.

Major, R A.M.C., T.F. Served in England, Egypt, Mesopotamia and France, 1914–19. Long Fox Memorial Lecturer, 1925. Chadwick Lecturer, 1927. Lumleian Lecturer, 1930.

John Elder MacIlwaine, 1874–1930

B.Sc. (Engineering) 1894. M.B., 1901 ; M D., 1904 ; D.P.H., 1907.

Physician, Royal Victoria Hospital, Belfast, 1910–29. Professor of Materia Medica and Therapeutics, Queen's University, Belfast, 1921–28.

Irish Rugby International, 1897–99.

Dresser, Irish Hospital, South Africa, 1899–1900. Physician, St. John's Ambulance Brigade Hospital, France, 1915–17.

The First Annual Meeting of the Cardiac Club was held at University College Hospital, London, under the chairmanship of Sir Thomas Lewis on November 22, 1922 and, subsequent meetings have been held on the day previous to the annual meetings of the Association of Physicians, wherever the Association happened to meet.

Many subjects have been discussed by the Club: the heart in the acute infections ; hyperpiesis ; angina pectoris ; infarct of the heart ; heart block ; the heart in pregnancy ; cardiac asthma , vaso-vagal attacks ; the treatment of œdema ; etc. In addition to the set subjects many short discussions upon case records, electrocardiograms, pathological specimens, etc., have also taken place, to the obvious pleasure of the members. On several occasions demonstrations have been given to the Club by those working in the laboratories. A list of the main subjects discussed at each meeting follows with the names of those who introduced the discussion.

In addition to the value the members have received from the meetings, the most important function of the Club has been the promotion of friendship between the members. All of us, from time to time, have received help from our confrères by advice or the supply of information or material. On two occasions the Club has been responsible for the mass collection of material from the members, from which important conclusions were drawn and made public at an earlier date than would have been possible if all the data had been dependent upon one observer We refer to Hay's paper upon the value of quinidine in the treatment of auricular fibrillation and to Gibson's paper upon ischæmic necrosis of the heart. It seems desirable that this procedure should be repeated as occasion demands.

Webb's egg has grown and the stripling is thriving. Under the new constitution we anticipate a strong and healthy adult life.

JOHN COWAN AND OTHERS

GENERAL MEETINGS OF THE CARDIAC CLUB

1922.	April 22.	Oxford Decision to form the Cardiac Club	Chairman,	A. G. Gibson
1922.	November 22.	University College Hospital, London First General Meeting	,,	Sir Thomas Lewis
1923.	May 17.	Edinburgh	,,	W. T. Ritchie
1924.	June 5.	Bristol	,,	Carey Coombs
1925.	May 28	Royal Soc of Medicine, London	,,	T. F. Cotton
1926.	May 20.	Newcastle	,,	W. E. Hume
1927.	June 2.	Belfast	,,	J. E. MacIlwaine
1928.	May 24.	Liverpool	,,	John Hay
1929.	April 4.	Cambridge	,,	A. N. Drury
1930	June 5.	The London Hospital, London	,,	John Parkinson
1931.	May 21.	Manchester	,,	Crighton Bramwell
1932.	May 12	Liverpool	,,	John Hay
1933	April 6.	Glasgow	,,	G. A. Allan
1934.	May 7.	Leeds	,,	Wardrop Griffith
1935.	June 6.	St. Thomas Hospital, London	,,	Sir Maurice Cassidy
1936.	May 28.	Manchester Fifteenth and last General Meeting of the Cardiac Club.	,,	Crighton Bramwell
1937	January 8.	An Extra-Ordinary Meeting was held at Guy's Hospital, London (Chairman; Bramwell) at which it was decided that the Cardiac Club should be transformed into the Cardiac Society of Great Britain and Ireland.		

MAIN SUBJECTS OF DISCUSSION

1922.	Infective Endocarditis	Sir Thomas Horder
1923.	The Use of Quinidine	Hay and Parkinson
	Abnormal QRST Complexes	MacIlwaine
1924.	The Heart in Pneumonia	Wardrop Griffith
	Digitalis	Fraser and Andrus (introduced).
	The Effect of Adrenalin on the Heart	Hume and Fraser
	Heard Disease in Children	Cotton and Carey Coombs
1925.	Anæmic Necrosis of the Heart	Gibson
	Simple Tachycardia	Parkinson
	Blood Pressure	Bramwell and Carey Coombs
	Cardiovascular Syphilis	Cotton
1926.	The Heart in Hyperpiesis	Wilkinson
	Angina Pectoris	Starling
1927.	Heart Block	Kennedy
	Treatment of Œdema	Patterson
1928.	Angina Pectoris	Ritchie
	Injection of the Coronary Arteries	John Campbell (introduced)
1929.	Cardiac Asthma	Fraser and Emmanuel
	Vaso-vagal Attacks	Starling
1930.	Mitral Stenosis	Cowan
	The Heart and Athletics	Bramwell
1931.	Ætiology of Heart Disease	Carey Coombs
1932.	The Heart in Diphtheria	Hume and Wilkinson
	The Heart in Influenza	Herapath
	The Influence of Tobacco	Maurice Campbell
	The Influence of Alcohol	Patterson
1933.	Abnormalities of the T wave	Cowan and Allan
	Right and Left Ventricular Complexes	Drury
1934.	Diseases of the Pulmonary Artery	Parkinson and Bedford
	Vaso-motor Angina	Cassidy and Patterson
1935.	Heart Symptoms and Gall Bladder Disease	Cotton and Hume
	Cardiac Disease of Unknown Ætiology	Stott and Maurice Campbell
1936.	Heart Disease and Pregnancy	Bramwell
	Heart Block	Gilchrist

(British Heart Journal, Vol. 1, No. 1, January, 1939)

THE CARDIAC SOCIETY

After the meeting of the Cardiac Club in 1935 it was suggested that, with the increasing numbers who were interested in Cardiology, the time might have come for expanding into a larger and more representative society and that the Executive should consider this possibility.

At the 1936 meeting in Manchester a memorandum which had been drawn up by the Executive (Allan, Bedford, Drury and Wilkinson) provoked a long discussion. After general approval of the principle of expansion the following committee was appointed to draw up a scheme for submission to a special meeting of the club.

Members: Evan Bedford, Crighton Bramwell, F. R. Fraser, John Parkinson and Maurice Campbell (Secretary)

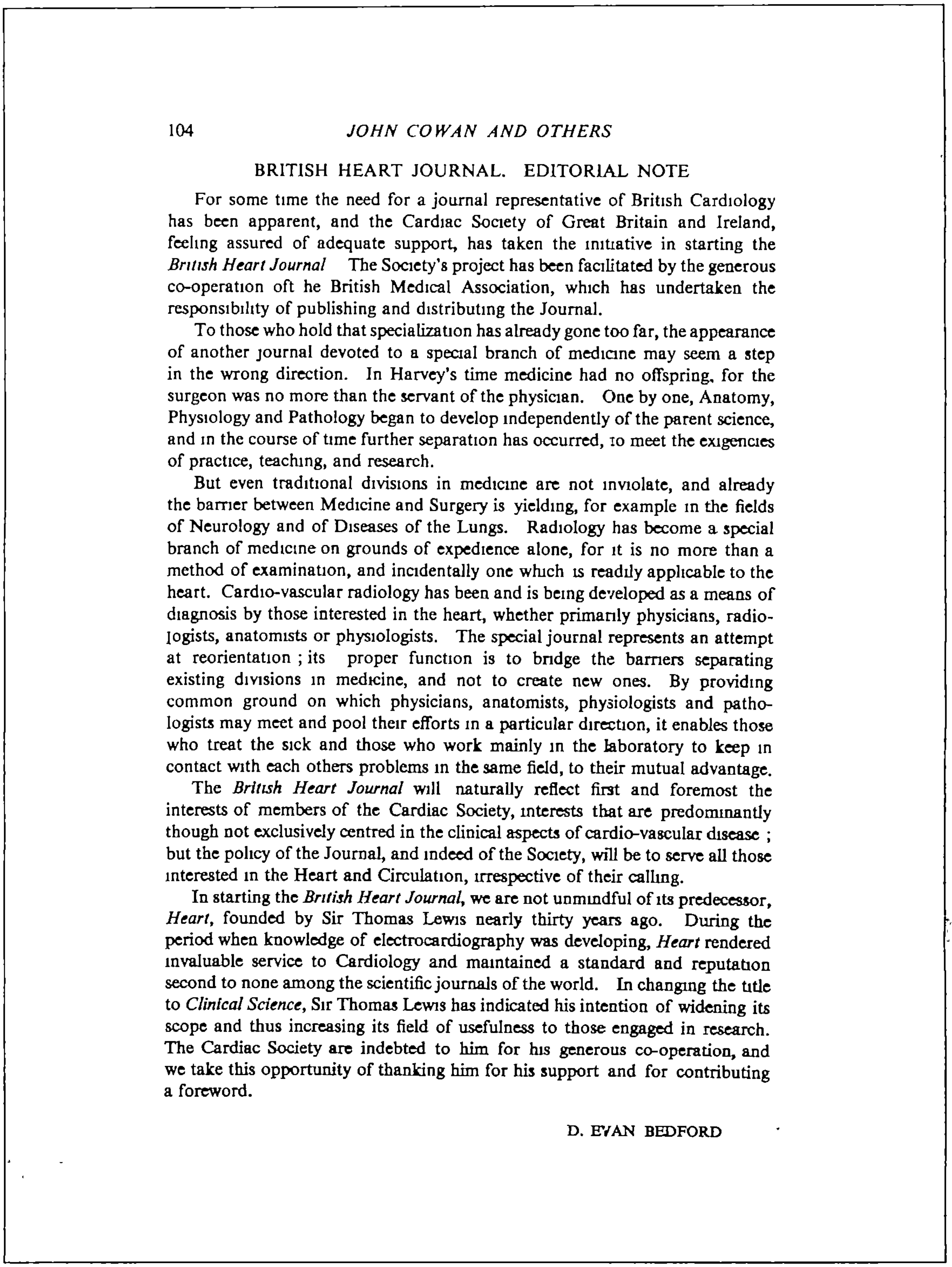
The committee held several meetings and drew up a draft constitution and rules for the Cardiac Society, and lists of names of those who should be invited to be Honorary, Extra-Ordinary, Ordinary and Associate members.

The last meeting of the Cardiac Club was a special one held in the Governor's Committee Room at Guy's Hospital on January 8, 1937. It was decided to accept these proposals for the formation of the new society, for its rules and constitution, and for the names of those who were invited to be the original members. The following were chosen as the first Council . Allan, Evan Bedford, Crighton Bramwell, Gilchrist (President 1937), Parkinson, Wilkinson and Maurice Campbell (Secretary and Treasurer).

At the First Annual Meeting of the Cardiac Society, held at Edinburgh on April 15, 1937, practically all the members attended, and in addition to the scientific business a committee was appointed to consider the possibility of starting a journal dealing with cardiology. *Members* · Gibson (Chairman), Evan Bedford, Maurice Campbell, Fraser and Wilkinson.

Several meetings were held, and in February 1938 the committee reported to the Council. They recommended that such a journal should be started and that the British Medical Association should be asked to publish it, as after various negotiations and meetings they thought that the British Medical Association were able and willing to publish a journal that would meet the needs of the Society. These recommendations were approved by the Council of the Cardiac Society, which appointed the Editors and the Editorial Board for the Journal. The title which has been chosen was suggested at an early stage, but many other titles have had their supporters The action the Council had taken with reference to the Journal was approved by the Society at its Second Annual Meeting at Bristol on June 2, 1938

MAURICE CAMPBELL,
Secretary of the Cardiac Society



BRITISH HEART JOURNAL. EDITORIAL NOTE

For some time the need for a journal representative of British Cardiology has been apparent, and the Cardiac Society of Great Britain and Ireland, feeling assured of adequate support, has taken the initiative in starting the *British Heart Journal* The Society's project has been facilitated by the generous co-operation oft he British Medical Association, which has undertaken the responsibility of publishing and distributing the Journal.

To those who hold that specialization has already gone too far, the appearance of another journal devoted to a special branch of medicine may seem a step in the wrong direction. In Harvey's time medicine had no offspring, for the surgeon was no more than the servant of the physician. One by one, Anatomy, Physiology and Pathology began to develop independently of the parent science, and in the course of time further separation has occurred, to meet the exigencies of practice, teaching, and research.

But even traditional divisions in medicine are not inviolate, and already the barrier between Medicine and Surgery is yielding, for example in the fields of Neurology and of Diseases of the Lungs. Radiology has become a special branch of medicine on grounds of expedience alone, for it is no more than a method of examination, and incidentally one which is readily applicable to the heart. Cardio-vascular radiology has been and is being developed as a means of diagnosis by those interested in the heart, whether primarily physicians, radiologists, anatomists or physiologists. The special journal represents an attempt at reorientation ; its proper function is to bridge the barriers separating existing divisions in medicine, and not to create new ones. By providing common ground on which physicians, anatomists, physiologists and pathologists may meet and pool their efforts in a particular direction, it enables those who treat the sick and those who work mainly in the laboratory to keep in contact with each others problems in the same field, to their mutual advantage.

The *British Heart Journal* will naturally reflect first and foremost the interests of members of the Cardiac Society, interests that are predominantly though not exclusively centred in the clinical aspects of cardio-vascular disease ; but the policy of the Journal, and indeed of the Society, will be to serve all those interested in the Heart and Circulation, irrespective of their calling.

In starting the *British Heart Journal*, we are not unmindful of its predecessor, *Heart*, founded by Sir Thomas Lewis nearly thirty years ago. During the period when knowledge of electrocardiography was developing, *Heart* rendered invaluable service to Cardiology and maintained a standard and reputation second to none among the scientific journals of the world. In changing the title to *Clinical Science*, Sir Thomas Lewis has indicated his intention of widening its scope and thus increasing its field of usefulness to those engaged in research. The Cardiac Society are indebted to him for his generous co-operation, and we take this opportunity of thanking him for his support and for contributing a foreword.

D. EVAN BEDFORD

(British Heart Journal, Vol. 1, No. 1, January, 1939)

Br Heart J 1987;57:11–16

Editorial

Risk factors for ischaemic heart disease in British men

A G SHAPER, S J POCOCK

From the Department of Clinical Epidemiology and General Practice, Royal Free Hospital School of Medicine, London

Being "top of the league" may be heartwarming for footballers but in the world of ischaemic heart disease it brings cold comfort. Northern Ireland, Scotland, and England and Wales are currently among the leaders for mortality rates from ischaemic heart disease both for men and women. While some countries, such as the United States, Australia, Canada, and New Zealand, have shown impressive declines in mortality rates for men over the past decade or so, the rates in the United Kingdom have shown little change. Improvements in the management of ischaemic heart disease, both medical and surgical, have considerably alleviated the suffering of many patients, but they are unlikely to bring about major reductions in the overall population risk of death or disability from ischaemic heart disease. We have become accustomed to being a high risk community and we can either continue in this frame of reference or we can recognise that a national policy for the prevention of ischaemic heart disease is needed urgently.

The administration of lime juice to prevent scurvy and the removal of the Broad Street pump handle to stop the spread of cholera are much quoted examples of successful action that preceded "adequate" information about a health hazard. The complexity of ischaemic heart disease and the controversies surrounding its aetiology and management, however, have raised the level of certainty demanded before action can be taken. Even though national committees of many countries have produced reports recommending action in various directions—almost all affect diet, cigarette smoking, blood pressure, and physical activity—there is still considerable argument about the extent to which these measures would affect the impact of ischaemic heart disease in our own community. Any rational approach to preventive action in the United Kingdom requires adequate information about the nature of ischaemic heart disease in this country. Much sound epidemiological data have already been provided by American studies such as Framingham[1] and by the study of London-based civil servants in Whitehall.[2] A more complete insight into the problem would require information on the prevalence and development of ischaemic heart disease in a representative sample of the whole British population of middle aged men. Accordingly, the British Regional Heart Study was initiated in 1978 as a prospective study of ischaemic heart disease in 7735 men aged 40–59 drawn at random from general practice registers in 24 towns in England, Wales, and Scotland. The aims of the study were: *(a)* to determine the reasons for the considerable geographic variation in mortality rates from ischaemic heart disease; *(b)* to provide information on the prevalence and incidence rates of the disease in British men; *(c)* to measure the effect of various factors (both personal and environmental) on the risk of developing ischaemic heart disease; *(d)* to relate this information to policies for the prevention and control of ischaemic heart disease.

It is perhaps necessary to remind readers that no national data of this kind were available and that most previous studies were only of specific occupational groups. The British Regional Heart Study provided a sample representing all socioeconomic classes and included men irrespective of their health or employment status. After extensive intial screening in 1978–80 all 7735 men have been followed for subsequent development of ischaemic heart disease, both fatal and non-fatal. Some men have moved from the original 24 practices, so that contact has had to be maintained with 800 additional practices. At their fifth year in the study 98% of

Requests for reprints to Professor A G Shaper, Department of Clinical Epidemiology and General Practice, Royal Free Hospital School of Medicine, Rowland Hill Street, London NW3 2PF surviving men satisfactorily completed a questionnaire on their risk factors, and health status.[3] As of July 1985, 336 men have had a major ischaemic event of which nearly half were fatal.

Prevalence of ischaemic heart disease

One in four of these middle aged men had some evidence of ischaemic heart disease at the initial examination. This was based on the World Health Organisation chest pain questionnaire and a resting electrocardiogram.[4] The prevalence of ischaemic heart disease varied between towns, from 17% (Lowestoft) to 30% (Merthyr Tydfil). There was a strong correlation between these prevalence rates and the mortality rates for ischaemic heart disease derived from official sources. This suggests that the geographic inequalities in mortality rates from ischaemic heart disease are genuine and not simply due to differences in case-fatality rates.

Unrecognised or silent myocardial infarction seems to be a genuine and highly underestimated problem. Only half of those with definite myocardial infarction on electrocardiogram had ever experienced chest pain suggestive of angina or possible myocardial infarction. Furthermore, only one in five of those with evidence of ischaemic heart disease could recall such a diagnosis having been made by a doctor and these were overwhelmingly the most seriously affected.[5] This low level of awareness of existing symptoms and signs among patients and doctors may account for the common belief that major ischaemic episodes "come from the blue". Little wonder that anticipatory care is not common.

Risk factors

The British Regional Heart Study has provided a national view of many established and potential risk factors for ischaemic heart disease among middle aged men.[6-8] A notable finding has been the very wide range of mean blood pressures observed, from 136 mm Hg systolic in Guildford and Shrewsbury to 153 mm Hg in Dunfermline.[6] In individual men, age, body mass index, and alcohol intake were important determining factors, with body mass index affecting blood pressure to a much greater extent than alcohol. Despite earlier claims by others that exposure to lead may have a hypertensive effect, blood lead concentrations did not appear to be a determinant of blood pressure in these British men.[9] Further studies to explore these regional differences in blood pressure are under way to find out why blood pressure rises with age and why it does so at different rates in the various towns.

Cigarette smoking also differed considerably between towns, from 12% smoking 20 or more per day in Guildford to 36% in Grimsby.[7] Although manual workers consistently had higher rates of cigarette smoking than non-manual workers, the difference in smoking rates between towns was more apparent than the differences between the social classes within the towns. Town "culture" may play a more crucial role in determining smoking (and drinking) rates than socioeconomic class. Rates of cigarette smoking were lowest in men who were light drinkers (1–2 drinks per day) and this may in part explain the reported lower risk of ischaemic heart disease in light drinkers.

The mean concentration of serum total cholesterol did not vary much between towns and did not relate to the town levels of ischaemic heart disease mortality. Although the observation brings some joy to those weary of or opposed to the "blood cholesterol story", it must be pointed out that the serum total cholesterol concentrations are uniformly high throughout Britain (mean 6·3 mmol/l)[8] and are considerably higher than concentrations in the United States.[10] The important message to be deduced from the British concentrations of serum total cholesterol is that we are a nation at considerable risk of ischaemic heart disease.

Risk of ischaemic heart disease

The first follow up analysis of major events in these British men confirms that the three most important risk factors are serum total cholesterol, cigarette smoking, and blood pressure.[11] Serum total cholesterol has a continuous positive association with risk of ischaemic heart disease, and men with high concentrations (>7·2 mmol/l) had three times the risk of men with low levels (<5·5 mmol/l). Of more importance is the observation that men with average concentrations (the typical British "man in the street") have double the risk of a major ischaemic event than those with lower concentrations of serum total cholesterol. This means that 60% of middle aged British men are at increased risk of ischaemic heart disease solely because of their serum total cholesterol concentrations.

Current cigarette smokers had the expected threefold increase in risk compared with men who had never smoked and there was a clear gradient of relation with the amount smoked. The observation that risk was also increased in ex-cigarette smokers (to at least twice that in those who had never smoked) is also of considerable importance.

Systolic and diastolic blood pressure were both important in predicting a major event and we sympathise with those who wonder why the diastolic pressure receives so much more attention in routine clinical practice. Work in progress on British Regional Heart Study data strongly indicates that systolic blood pressure alone is a far more reliable predictor of risk of cardiovascular disease than diastolic blood pressure alone. Men with systolic blood pressures just below the usually accepted levels of hypertension (148–160 mm Hg) still had a twofold higher risk of a heart attack than men with lower blood pressures. This emphasises the importance of regarding blood pressure as a continuously distributed variable and also highlights the widespread nature of this risk factor in British men.

Overweight (body mass index), serum triglycerides, and high density lipoprotein (HDL) cholesterol were not predictive of risk after allowance for the other factors had been made by multivariate analysis. This is not to say that they are not important in the development of ischaemic heart disease but merely that their importance as predictors is ultimately overshadowed by other factors. The risk of a heart attack is twice as high in overweight men as in lean men, but this can be attributed to their raised concentrations of serum total cholesterol and blood pressure at screening which outrank, in statistical terms, the presence of overweight. Nevertheless, it is evident that longterm overweight and its determinants must have been critical in the ultimate development of risk. We need to find better ways of expressing the importance of factors such as overweight that at present lose their importance in the process of multivariate analysis.

High density lipoprotein cholesterol

As in other prospective studies, the risk of a heart attack in British men with the lowest concentrations of HDL cholesterol (<0·93 mmol/l) is twice that in men with higher concentrations (>1 06 mmol/l). HDL cholesterol is negatively associated with cigarette smoking and with non-HDL cholesterol, both of which have much stronger positive associations with the risk of major ischaemic heart disease events. Thus in multivariate analysis, HDL cholesterol does not emerge as having independent predictive ability.[12] Although at first sight this seems at odds with the importance accorded to HDL cholesterol by other workers, comparison with six other prospective studies suggests that the findings of the British Regional Heart Study are similar to those of almost all other studies. All show that HDL cholesterol concentrations are lower in men with ischaemic heart disease than in other men, but only in Tromso, the first and the smallest of the studies, is the effect a striking one. It seems likely that closer attention to the concurrent effect of other factors on HDL cholesterol and on the risk of ischaemic heart disease may reduce the predictive importance of HDL cholesterol in these studies. The response to these "discrepant" findings has been vigorous, and criticism has been focused on the precision of measurement of HDL cholesterol and other methodological issues.[13 14] In reply, attention has been drawn to the internal consistency of the data, with HDL cholesterol in the British Regional Heart Study showing the same relation to alcohol, smoking, body mass index, triglyceride, and non-HDL cholesterol as seen in other studies.[14] There is no doubt that low HDL cholesterol is a risk factor for ischaemic heart disease, albeit not an independent one, and equally no doubt that HDL cholesterol is a critical factor in lipid transport and thus in the development of ischaemic heart disease. What is in question is its independent ability to predict heart attacks and to "protect" against such events.

Other risk factors

Thus far, attention has been focused on the standard risk factors. Now that all men have completed at least five years follow up a further analysis of the considerably increased number of major ischaemic heart disease events allows for a full evaluation of other risk factors. These include family history, diabetes mellitus, serum glucose and uric acid concentrations, personality characteristics (type A), physical activity, electrocardiographic findings, alcohol intake, respiratory disease, blood groups, and a wide range of biochemical and haematological measurements. We have already found a way of using the relatively simple information available on physical activity to derive a score that is related to the occurrence of heart attacks. Whether this will survive the rigorous assault of multivariate analysis remains to be seen. The data on alcohol intake are of particular importance because intake has been validated against 24 biochemical and haematological measurements.[15] Our preliminary findings do not support the claim that regular moderate alcohol consumption has a protective effect against ischaemic heart disease.

Risk factors and pre-existing ischaemic heart disease

There is considerable controversy about whether the established risk factors continue to exert an influence in those men in whom evidence of ischaemic heart disease has already developed. There is no doubt that the presence of ischaemic heart disease in terms of angina, previous myocardial infarction, or electrocardiographic abnormalities (ischaemia, infarction) constitutes a considerable risk for a subsequent major event. Logically, therefore, the independent predictive role of the risk factors (serum total cholesterol, smoking, blood pressure) *must* be proportionately reduced in those with pre-existing ischaemic heart disease. In the British Regional Heart Study men with and without pre-existing ischaemic heart disease who became "cases" (that is manifested major ischaemic heart disease events) had similar levels of risk factors, which suggests that these factors continue to exert an influence in all subjects.[11] Furthermore, men with pre-existing ischaemic heart disease who did *not* become "cases" had lower levels of systolic and diastolic blood pressure, body mass index, serum total cholesterol, trigylcerides, and percentage current cigarette smokers and higher concentrations of HDL cholesterol than men with pre-existing ischaemic heart disease who became "cases". When the men with and without pre-existing ischaemic heart disease were separated, multivariate analysis showed that some established risk factors (total cholesterol, blood pressure) continued to make an important independent contribution to risk. This implies that attention to these risk factors could be of importance in reducing subsequent risk in men who already have evidence of heart disease. Support for this concept is found in the Belgian Heart Disease Prevention Project, where the results of multifactorial intervention were strikingly more effective in men with electrocardiographic evidence of ischaemia at baseline examination than in men with a normal electrocardiogram at baseline.[16]

Ischaemic heart disease without risk factors?

A view that is widely held by cardiologists is that they see many patients with major ischaemic events who do not have identifiable risk factors. In the British Regional Heart Study at least a twofold *independent* increase in risk was associated with any *one* of the following criteria: *(a)* serum total cholesterol $\geqslant 6$ mmol/l, *(b)* systolic blood pressure $\geqslant 148$ mm Hg or diastolic blood pressure $\geqslant 93$ mm Hg, or *(c)* current cigarette smoking. Only five of the 202 cases of ischaemic heart disease had none of these risk criteria and in over two thirds at least two criteria were present.[11] Of the five men with none of the above criteria present, three had evidence of pre-existing ischaemic heart disease. The belief that major ischaemic heart disease occurs not infrequently in the absence of identifiable risk factors is perpetuated by a failure to recognise that even moderate increases in blood lipids and blood pressure carry an excess risk of ischaemic heart disease, especially if a man smokes cigarettes.

Identifying men at high risk

The ultimate aim of the British Regional Heart Study is to help to reduce the impact of ischaemic heart disease on our society, and currently a major issue is what action should we take in response to the current epidemic of ischaemic heart disease. Although there is growing agreement that many major changes in lifestyle are required, with changes in diet, cigarette smoking, and physical activity, there is an awareness that such changes as we are likely to make in the foreseeable future are unlikely to lead to dramatic or immediate changes in our present high rates of ischaemic heart disease mortality. We have therefore used the British Regional Heart Study data to explore the possibility of identifying those at *highest* risk of major ischaemic heart disease events, so that they may receive appropriate medical care. A relatively simple method has been devised which does not require measurement of blood lipids or electrocardiography and can be readily carried out on an opportunistic basis in general practice and in other situations, including cardiology clinics.[17] All that is required is a knowledge of whether the man has been told by a doctor that he has ischaemic heart disease (angina, myocardial infarction) or diabetes or both and whether a parent has died of "heart trouble". In addition, blood pressure and the number of smoking years need to be determined. From this information a score can be calculated and compared with various cut off points derived from the British Regional Heart Study. This system will identify a group of men, the top 20% of the overall risk score distribution, in which more than half of the new episodes of major ischaemic heart disease taking place in the five years after screening will occur. Addition of serum total cholesterol and electrocardiographic findings to this score only slightly improves the identification of high risk men and greatly increases the cost and effort of screening. It is considered that this strategy of identifying high risk people will be a useful complement to the population approach of changing life styles, and will help to prevent premature deaths and to increase public and professional awareness of the size of the problem and the need for preventive action.

Geographical variations in ischaemic heart disease

Some of the initial impetus for the British Regional Heart Study came from a concern that the quality of drinking water (for example its hardness) was an important and potentially modifiable risk factor in ischaemic heart disease and one which might account for the considerable regional variation in mortality from ischaemic heart disease. We have shown that water hardness is independently associated with ischaemic heart disease mortality rates to about the same extent as temperature, rainfall and socioeconomic status.[18] The magnitude of the effect is small compared with the effects of other risk factors such as cigarette smoking or blood pressure. Although the water story plays some small role in regional variations in ischaemic heart disease mortality, such variations are explained to a greater extent by the regional differences in cigarette smoking and blood pressure levels.[19]

One of the most interesting findings in the British Regional Heart Study has been the difference in mean blood pressure levels between towns. This is associated with corresponding differences in the rates of systolic and diastolic hypertension, of doctor-diagnosed hypertension, and of regular treatment for high blood pressure. The reasons for differences in blood pressure levels and rates of hypertension between communities has usually been explored on an international basis and this leads to major methodological problems. The nomads of northern Kenya and the highlanders of New Guinea (with low blood pressures) differ from the inhabitants of New York or London (with high blood pressures) in too many ways to allow causality to be readily attributed to any of the differences observed between these very disparate groups. The British Regional Heart Study provides an opportunity to explore the inter-town differences within Britain. The intention is to determine at what age the blood pressure levels in these different communities diverge from one another and what factors, personal or environmental, feature in this divergence.

Conclusion

There have been remarkable achievements in both the medical and surgical aspects of cardiology that excite the imagination and stir enthusiasm for further high technology developments. To suggest that these achievements are irrelevant to the persistently high incidence of ischaemic heart disease seems ungrateful. Attempts to prevent ischaemic heart disease do not inspire the same fervour; there are no immediate rewards for individuals or communities. The outcome of any prevention policy is likely to be a very gradual decrease in a risk that has become accepted as normal. There will be no moment for flags or trumpets. In media terms, a man with a transplanted heart far outranks the unidentifiable man who has avoided a heart attack because of preventive measures.

There is no simple answer to the prevention of ischaemic heart disease and each country will encounter different problems, depending on the distribution of the major risk factors and on varying public and professional attitudes. Each country needs to establish the magnitude and the nature of its own ischaemic heart disease problem, although it will derive considerable benefit from the experience and findings of studies carried out elsewhere. The evidence accumulating from all sources strongly suggests that the standard risk factors, serum total cholesterol, cigarette smoking, and blood pressure, play an overwhelming role in determining the incidence of ischaemic heart disease. Attempts to reduce the incidence by lowering serum total cholesterol or blood pressure in middle aged men, however, have met with limited success and certainly do not inspire doctors to vigorous action. The natural history of ischaemic heart disease strongly implicates the *duration* of exposure to the risk factors, and it seems likely that major changes in the incidence of ischaemic heart disease may require major changes in diet, smoking behaviour, and physical activity from an early age, as well as the prevention of hypertension. If we are to achieve these major changes, a sound national data base on risk factors for ischaemic heart disease is required in order to influence the public, doctors, and other professionals in their clinical and community work, and the legislators and administrators who provide and manage our resources. The data base may change from time to time, so that reassessment at regular intervals may be necessary. Attempts are being made to do so through the Monica studies[20] and through the Scottish Heart Health Study and Heartbeat Wales. All of these will contribute to a better understanding and to decisions on appropriate action.

References

1 Dawber TR. *The Framingham Study. The epidemiology of atherosclerotic disease.* Cambridge, Massachusetts: Havard University Press, 1980.

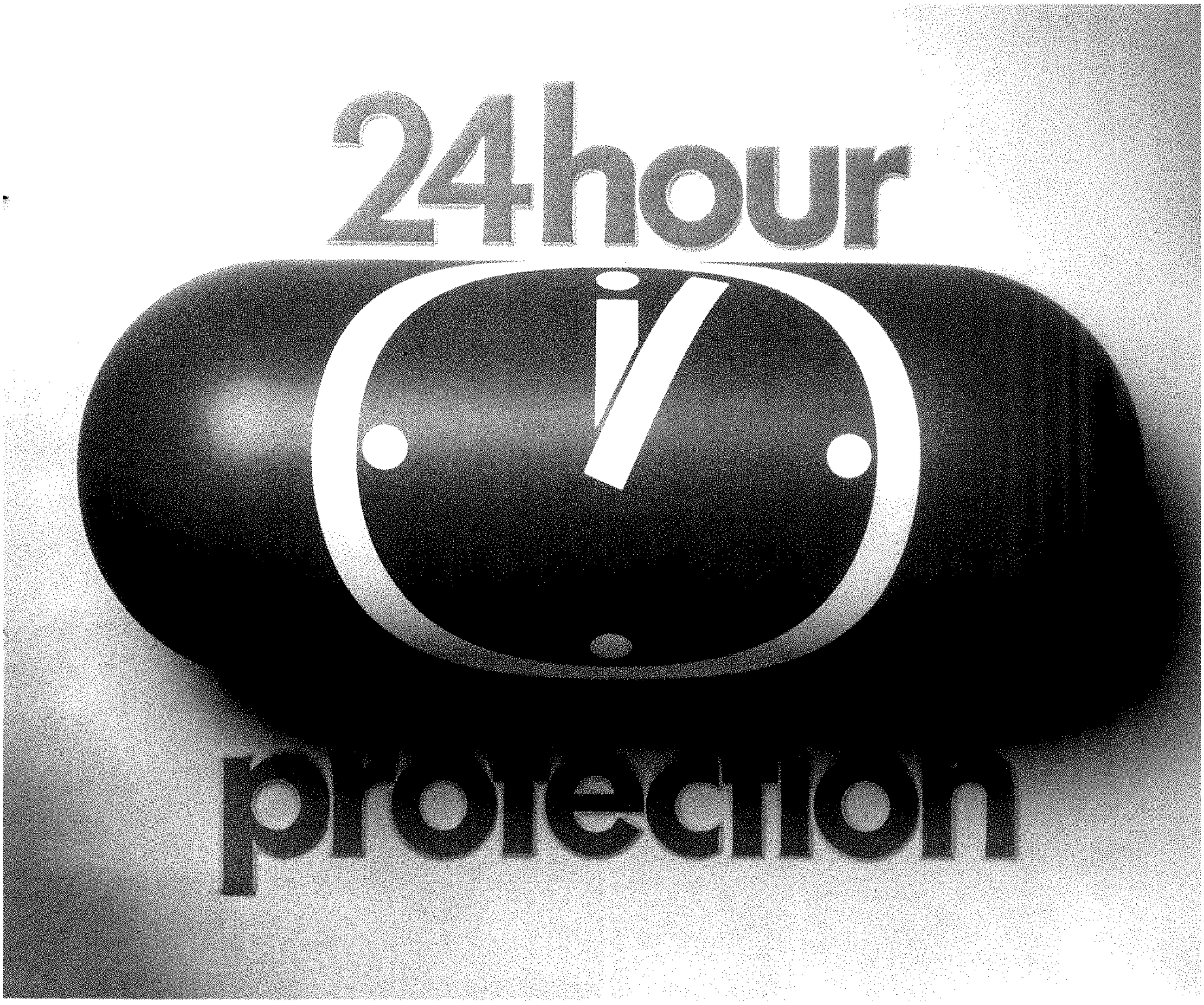
2 Rose G, Reid DD, Hamilton PJS, McCartney P, Keen H, Jarrett RJ. Myocardial ischaemia, risk factors and death from coronary heart disease. *Lancet* 1977;i:105–9.

3 Walker M, Shaper AG Follow-up of subjects in prospective studies in general practice. *J R Coll Gen Pract* 1984;34.365–70.

4 Shaper AG, Cook DG, Walker M, Macfarlane PW. Prevalence of ischaemic heart disease in middle aged British men. *Br Heart J* 1984;51.595–605.

5 Shaper AG, Cook DG, Walker M, Macfarlane PW. Recall of diagnosis by men with ischaemic heart disease. *Br Heart J* 1984;51:606–11.

6 Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale



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Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics

JOHN BAYLISS,* MICHAEL NORELL,† RUDOLPH CANEPA-ANSON,*
GEORGE SUTTON,† PHILIP POOLE-WILSON*

*From †Hillingdon Hospital, Uxbridge, Middlesex, and *the National Heart Hospital and Cardiothoracic Institute, London*

SUMMARY The clinical and neuroendocrine response to diuretic treatment was assessed at rest and on exercise in 12 patients with heart failure. Before treatment all patients were limited by breathlessness on exercise; one was oedematous. Plasma renin activity and aldosterone were normal but plasma noradrenaline was raised both at rest and on exercise. After one month's treatment with frusemide (40 mg) and amiloride (5 mg) weight was significantly reduced by a mean of 3·5 kg and exercise capacity had doubled. Plasma noradrenaline fell to normal at rest but remained abnormally raised on exercise. Plasma renin activity and aldosterone increased significantly both at rest and on exercise.

Diuretics bring about a considerable clinical improvement in patients with chronic heart failure but they stimulate the renin-angiotensin system. Activation of the renin-angiotensin system in moderate heart failure occurs as a response to diuretic treatment rather than as a result of the disease process itself.

Although diuretics are widely used in the treatment of chronic heart failure, the initial effects of treatment have rarely been studied. In recent years the importance of the neuroendocrine response to heart failure has been emphasised and many trials have been undertaken with drugs that oppose activation of the sympathetic and renin-angiotensin systems. Angiotensin converting enzyme (ACE) inhibitors in particular have been shown to be beneficial in patients with moderate to severe heart failure already treated with diuretics.[1] Diuretics are known to activate the renin-angiotensin system; so a raised renin activity in patients with heart failure may be a consequence of treatment rather than of heart failure itself. The benefit of ACE inhibitors may occur partly because these drugs offset this effect of diuretics.

We have studied untreated patients presenting with breathlessness due to chronic heart failure and have assessed clinical and neuroendocrine variables at rest and on upright exercise before and one month after the introduction of diuretics (frusemide and amiloride). The purpose of the study was to determine whether neuroendocrine systems were activated in untreated heart failure or whether activation was secondary to treatment.

Patients and methods

Twelve patients (mean age 59 years (range 22–75), five female) were studied. The aetiology of heart failure was coronary artery disease without recent myocardial infarction in six patients, dilated cardiomyopathy in five, and mitral valve disease in one. No patient had hypertensive or renal disease.

All patients had been referred with breathlessness on moderate exertion (New York Heart Association class II–III) but had received no treatment. Patients had had symptoms for between one and six months The patient with mitral valve disease had been on digoxin for control of atrial fibrillation, and the drug was continued. No other cardiac drugs were being taken by these patients. Five patients had sinus tachycardia at rest. The jugular venous pressure was elevated in four and a third heart sound was heard in seven. Mild pitting ankle oedema was present in one patient. Four patients were in atrial fibrillation. All patients had cardiomegaly by chest *x* ray (cardiothoracic ratio >0·55) or increased left ventricular

Requests for reprints to Professor P A Poole-Wilson, Cardiothoracic Institute, 2 Beaumont Street, London W1N 2DX.

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end systolic diameter (>5·5 cm) by echocardiography. All patients had radiological evidence of pulmonary venous hypertension.

Patients were initially assessed after resting for at least one hour. Four patients had been admitted to hospital. The remainder were studied as outpatients. Nude weight was measured. Heart rate was determined from an electrocardiogram. Venesection for neuroendocrine measurements was performed with the patient supine (see below). Patients performed a maximal treadmill exercise test at low workloads that increased in six-minute stages.[2] The electrocardiogram was observed continuously and venesection was repeated at maximal exercise. One patient was unable to walk on the treadmill because of breathlessness.

Treatment with frusemide 40 mg and amiloride 5 mg (Frumil 1 tablet) once daily was started. Inpatients were discharged after treatment. All patients were reviewed after four weeks. One patient suffered a transient cerebral ischaemic attack and was not restudied. The remaining 11 patients were reassessed on treatment at least four hours after their medication. Clinical and neuroendocrine measurements were made at rest and after maximal treadmill exercise. The exercise test was not repeated in the patient who had been unable to walk on the treadmill.

Venous blood for neuroendocrine measurements was taken into chilled tubes, centrifuged immediately, and the plasma stored at −70°C until assay. Plasma renin activity and aldosterone were measured by radioimmunoassay,[3 4] (normal range 0·5–2·5 ng/ml/h (0·39–1·9 nmol/l/h) and 100–600 pmol/l, respectively). Plasma noradrenaline was measured by radioenzymatic assay, with a modification of the method of Henry *et al* (normal range 200–800 pg/ml (1·2–4 7 nmol/l)).[5]

Mean values (SE) are given for weight, heart rate, and exercise time. Hormonal values were distributed normally only after logarithmic transformation, so geometric means (95% confidence limits) are given for these results. Statistical analysis was by analysis of variance.

Results

The clinical features of patients before treatment have been described above. After one month of treatment with diuretics the signs of heart failure were no longer present. In no patient was the jugular venous pressure elevated or an additional heart sound heard. Weight was reduced by a mean of 3·64 kg (p = 0·0003) (table). Resting heart rate fell (p = 0·03). Heart rate at maximal exercise remained unchanged. Mean maximal treadmill time before treatment was 9·1 min, corresponding on our exercise protocol to an oxygen consumption of approximately 17 ml of oxygen/kg/min. Maximal treadmill exercise time increased by 93% (p = 0·007) (fig 1). Whereas all patients had been limited by breathlessness on exercise before treatment, five patients were limited more by fatigue than by breathlessness when they exercised on treatment.

Plasma renin activity and plasma aldosterone in untreated patients were normal both at rest and at maximal exercise, but these values increased to abnormal concentrations after diuretic treatment (p < 0·0007) (table and figs 2 and 3). Plasma noradrenaline in untreated patients was raised at rest and at maximal exercise. After diuretic treatment plasma noradrenaline fell to normal at rest (p = 0·005), but remained abnormally raised on exercise (table and fig 4). The reduction in resting heart rate during diuretic treatment correlated with the reduction in resting plasma noradrenaline (r = 0·64, p =

Table *Clinical measurements (mean (SE))* and hormonal values (geometric mean (95% confidence interval))† before and after one month's treatment with frusemide 40 mg and amiloride 5 mg*

Variable	*Before diuretics* *Rest: n = 12* *Exercise: n = 11*	*After diuretics* *Rest: n = 11* *Exercise: n = 10*
Body weight* (kg)	72·4 (3·0)	68·5 (3·6)
Heart rate* (beats/min):		
Rest	89 (5)	75 (2)
Exercise	143 (5)	145 (4)
Exercise time* (min)	9·1 (2·0)	17·6 (2·3)
Plasma renin activity† (ng/ml/h):		
Rest	1·1 (0·8, 1·7)	4·2 (2·7, 6·6)
Exercise	2·5 (1·5, 4·2)	11·3 (6·0, 21·2)
Plasma aldosterone† (pmol/l)		
Rest	169 (122, 235)	488 (345, 690)
Exercise	223 (165, 301)	737 (556, 978)
Plasma noradrenaline† (pg/ml)		
Rest	712 (556, 912)	430 (336, 552)
Exercise	1865 (1350, 2576)	1421 (1075, 1879)

Conversion: traditional units to SI—plasma renin activity 1 ng/ml/h = 0·771 nmol/l/h; plasma noradrenaline 1 pg/ml = 5·9 pmol/l.

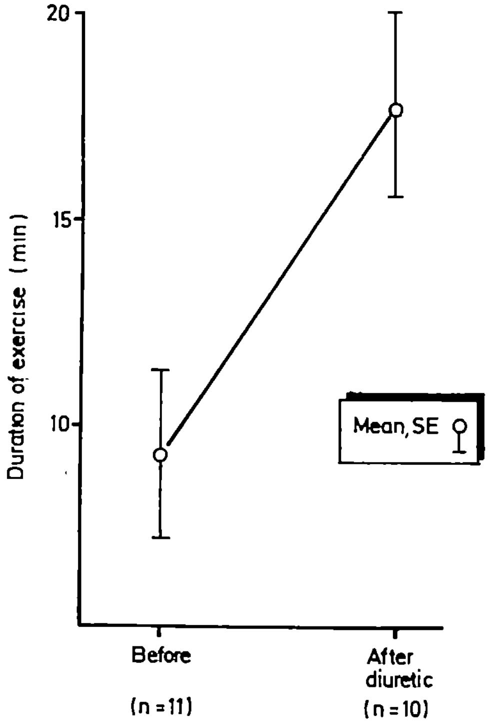


Fig 1 *Maximal treadmill exercise time in patients before and after diuretic treatment*

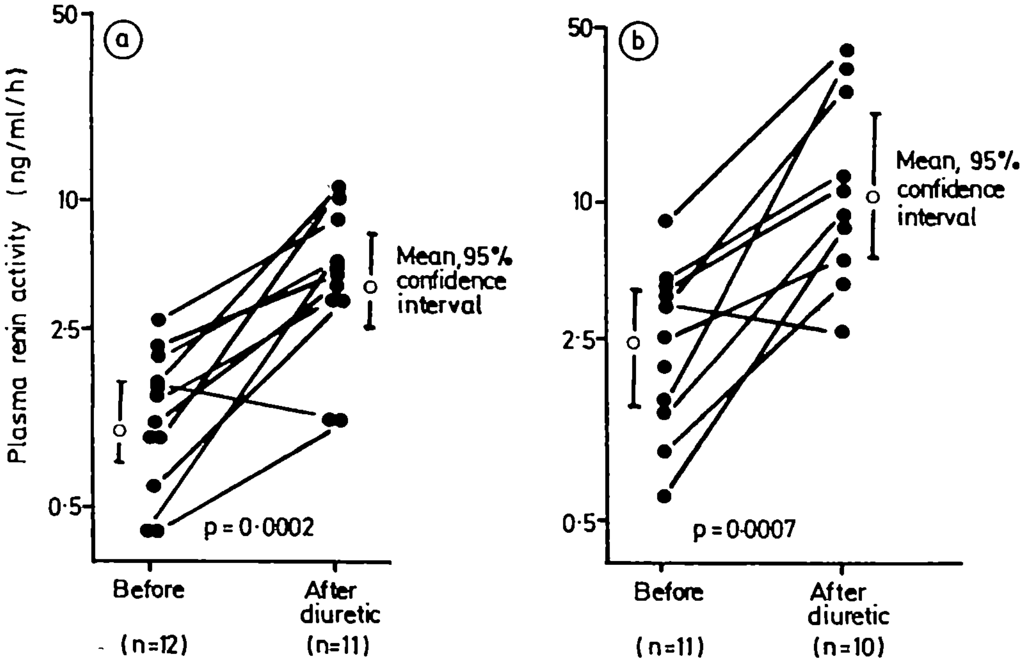


Fig 2 *Plasma renin activity at rest (a) and at maximal exercise (b) in patients before and after diuretic treatment. Conversion: traditional units to SI—renin: 1 ng/ml/h = 0·771 nmol/l/h.*

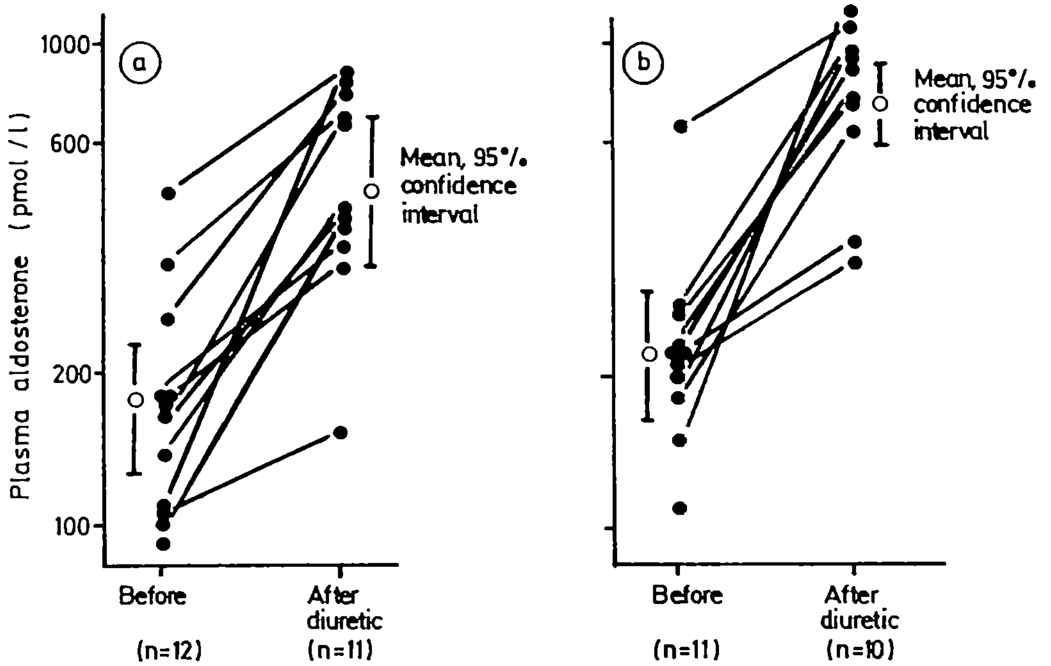


Fig 3 *Plasma aldosterone at rest (a) and at maximal exercise (b) in patients before and after diuretic treatment.*

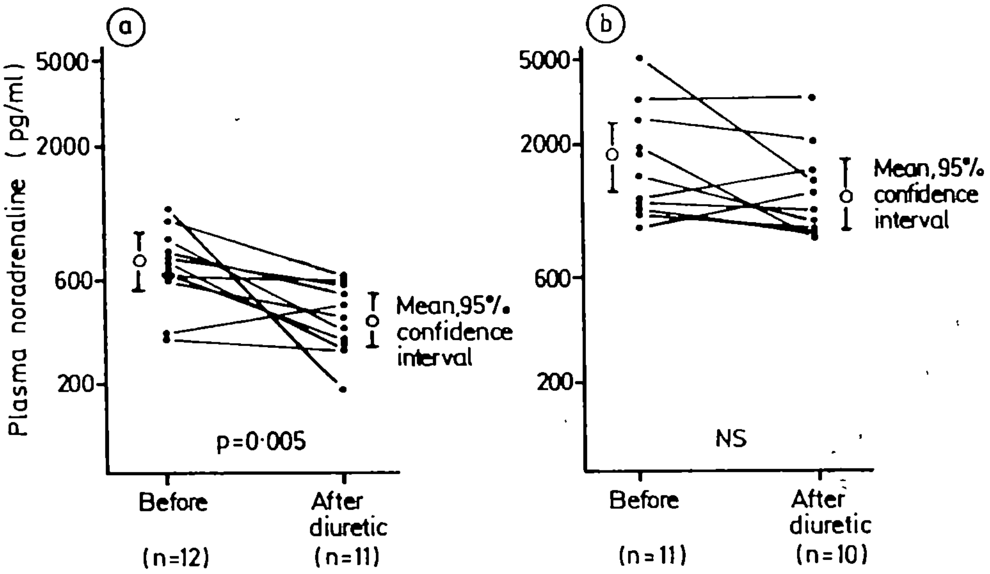


Fig 4 *Plasma noradrenaline at rest (a) and at maximal exercise (b) in patients before and after diuretic treatment. Conversion: traditional units to SI—noradrenaline: 1 pg/ml = 5·9 pmol/l.*

0·03), suggesting that plasma noradrenaline values were a measure of the degree of sympathetic activation.

Neuroendocrine variables in patients with heart failure due to coronary artery disease did not differ from those with dilated cardiomyopathy before treatment, and the response to diuretic treatment was similar. In the patient with mitral valve disease, plasma renin activity fell after diuretic treatment both at rest and on exercise, though plasma aldosterone was increased by diuretic treatment in this patient.

Discussion

In an early study of the hormonal response to chronic heart failure, Brown *et al* found that nine out of 13 patients with untreated left ventricular failure had normal or low plasma renin activity at rest.[6] Our study provides further evidence that not all untreated patients in heart failure have raised plasma renin activity or aldosterone concentrations at rest. We have also shown that the stimulus of maximal upright exercise causes only a modest increase in these hormones.

It is probable that the untreated patients in the present study had expanded circulatory volumes, as suggested by elevation of the venous pressure in four, peripheral oedema in one, and a loss of weight of more than 3 kg on treatment. In the presence of such circulatory expansion the finding of values for plasma renin activity at the upper end of the normal range does suggest some activation of this system. The present patients had only "moderate heart failure". In more severe untreated heart failure it is possible that activation of the renin-angiotensin system might be greater, but most previous studies showing significant activation of the renin-aldosterone system in heart failure are difficult to interpret as they have been undertaken in patients who not only had severe heart failure but were also being treated with diuretics. In such cases, raised concentrations of plasma renin and aldosterone could be due to the heart failure itself, to diuretic treatment, or to both.

In the present study plasma noradrenaline was raised both at rest and on exercise in untreated patients. Activation of the sympathetic system, as assessed by plasma noradrenaline concentration, appears to relate to the degree of left ventricular dysfunction in heart failure.[7 8] In our patients with "moderate" heart failure the increase in plasma noradrenaline was not associated with an increase of plasma renin activity, suggesting that the earliest neuroendocrine response to heart failure is activation of the sympathetic system alone.

Diuretic drugs are firmly established as the initial treatment for patients with chronic heart failure. Yet few studies have reported the long term effects of starting such treatment. In the only trial that has assessed patients on exercise, Stampfer *et al* found that the use of thiazide diuretics in patients with established heart failure caused a diuresis of 3·4 kg, resulting in clinical improvement and a slight increase in exercise capacity.[9] In Stampfer *et al*'s study cardiac output was reduced at rest (−20%) and on exercise (−10%) in all patients and this was attributed to a fall in ventricular filling pressure.[9] The ventricular filling pressure was reduced either as a result of venodilatation or because of a reduced circulating volume secondary to a diuresis. Several other studies[10−12] have demonstrated similar short term haemodynamic effects at rest. Such reduction in cardiac output with the use of diuretics is often associated with immediate stimulation of the renin-angiotensin system.[13] Ikram *et al*[14], Nicholls *et al*[15], and Knight *et al*[16] have shown that renin, angiotensin, and aldosterone continue to increase over several days as "dry weight" is achieved and cardiac output falls.

The present study has shown that the introduction of frusemide with amiloride in patients with untreated heart failure caused a pronounced increase in plasma renin activity and aldosterone at rest and on exercise. Despite this stimulation of the renin-angiotensin-aldosterone system there was clinical improvement and an increase in exercise capacity over a period of one month. Clinical improvement was associated with a reduction in sympathetic activity and plasma noradrenaline at rest but not on exercise.

Our study is complementary to that of Stampfer *et al*[9] on the effects of thiazide diuretics in heart failure. Although we did not make haemodynamic measurements, it is likely that the haemodynamic effects of treatment were similar to those reported by Stampfer *et al*[9], with reductions in left ventricular filling pressures and cardiac output at rest and on exercise. The initial improvement of breathlessness and increase in exercise capacity in our patients may have been due to relief of pulmonary congestion, but other mechanisms may be important in the longer term because breathlessness and maximal exercise capacity do not in general correlate with left ventricular filling pressure[17] in patients with chronic heart failure treated with diuretics. An alternative explanation for the increase in exercise capacity would be that despite an overall reduction in cardiac output, the diuresis brought about a greater fall in arteriolar resistance in skeletal muscle on exercise and thus increased muscle blood flow.

These results have an important clinical implication. It is possible that a further increase in exercise capacity might have been achieved in these untreated patients if an angiotensin converting enzyme inhibitor had been prescribed with the diuretic to limit the increase of renin activity. Prevention of the diuretic induced stimulation of the renin-angiotensin system may be important in the long term management of chronic heart failure, since stimulation of the renin-angiotensin system, causing vasoconstriction and fluid retention, is deleterious to the failing heart and circulation.[18 19]

P, 25, 732

The obvious clinical benefits of diuretics in chronic heart failure may mask more subtle, possibly adverse, neuroendocrine changes, which may have important long term consequences in the progression of the disease process itself.

References

1 Lipkin DP, Poole-Wilson PA. Treatment of chronic heart failure: a review of recent drug trials. *Br Med J* 1985;**291**.993–6.

2 Lipkin DP, Perrins J, Poole-Wilson PA. Respiratory gas exchange in the assessment of patients with impaired ventricular function. *Br Heart J* 1985;**54**: 321–8.

3 Roulston JE, MacGregor GA. Measurement of plasma renin activity by radioimmunoassay after prolonged cold storage. *Clin Chim Acta* 1978;**88**:45–8.

4 Jones VHT, Wilson GA. Determination of aldosterone in biological fluids. In: Reid E, ed. *Assay of drugs and other trace compounds in biological fluids. Methodological development in biochemistry*. Vol 5 Amersham: Elsevier, North Holland, 1976.149–58.

5 Henry DP, Starman BJ, Johnson DG. A sensitive radioenzymatic assay for norepinephrine in tissue and plasma. *Life Sci* 1975;**16**:375–84.

6 Brown JJ, Davies DL, Johnson VW, Lever AF, Robertson JIS. Renin relationships in congestive heart failure, treated and untreated. *Am Heart J* 1970;**80**:329–42.

7 Goldstein DS. Plasma norepinephrine as an indicator of sympathetic neural activity in clinical cardiology. *Am J Cardiol* 1981;**48**:1147–54.

8 Francis GS, Goldsmith SR, Cohn JN. Relationship of exercise capacity to resting left ventricular performance and basal plasma norepinephrine levels in patients with congestive heart failure. *Am Heart J* 1982;**104**:725–31.

9 Stampfer M, Epstein SE, Beiser GD, Braunwald E. Hemodynamic effects of diuresis at rest and during intense upright exercise in patients with impaired cardiac function. *Circulation* 1968,**37**:900–11.

10 Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJC. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction *N Engl J Med* 1973;**288**:1087–90.

11 Lal S, Murtagh JG, Pollock AM, Fletcher E, Binnion PF. Acute haemodynamic effects of frusemide in patients with normal and raised left atrial pressures. *Br Heart J* 1969;**31**:711–7.

12 Nelson GIC, Silke B, Ahuja RC, Hussain M, Taylor SH. Haemodynamic advantages of isosorbide dinitrate over frusemide in acute heart failure following myocardial infarction. *Lancet* 1983;**i**.730–2.

13 Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985;**103**:1–6.

14 Ikram H, Chan W, Espiner EA, Nicholls MG. Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure. *Clin Sci* 1980;**59**:443–9.

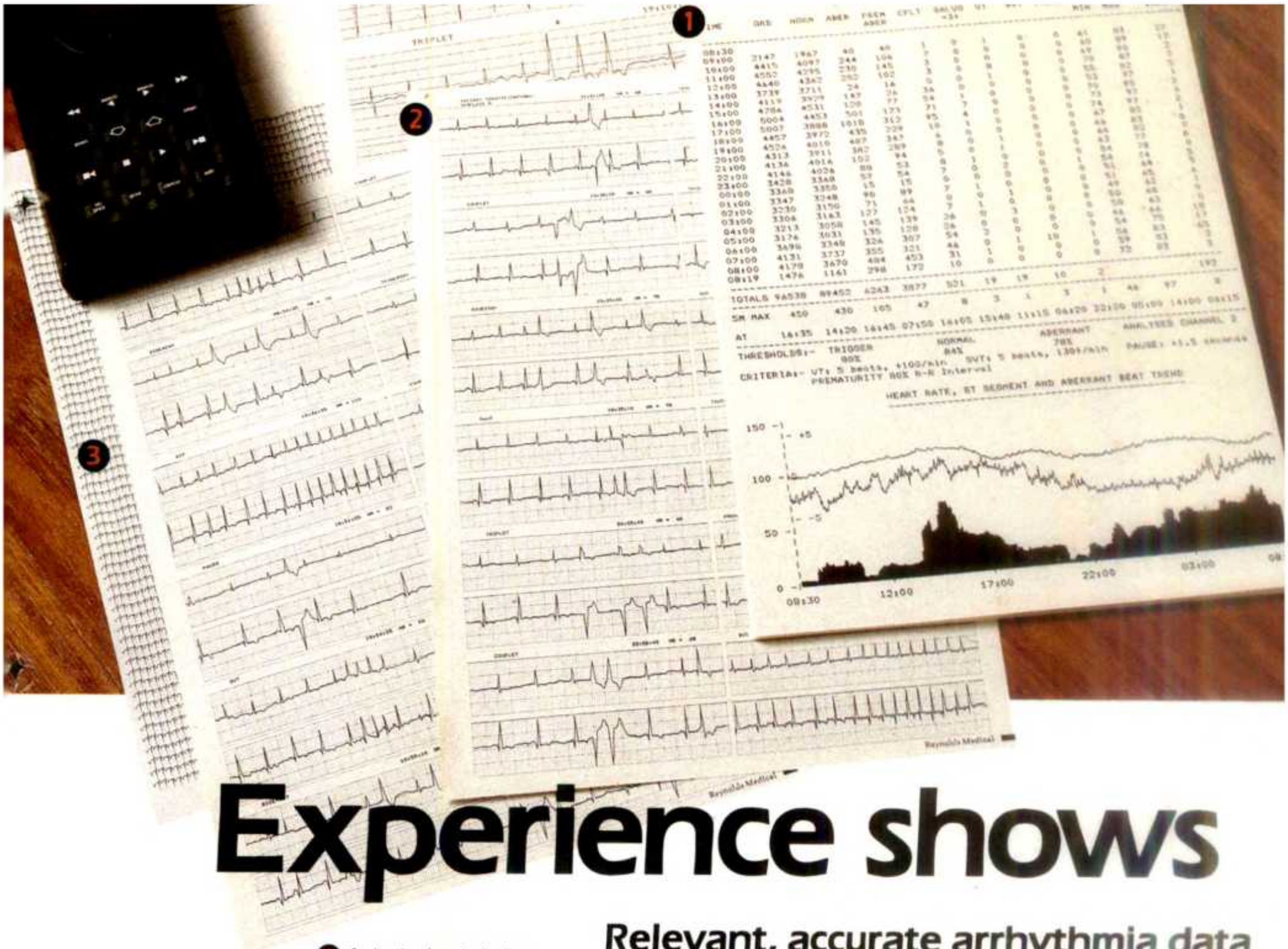
15 Nicholls MG, Espiner EA, Donald RA, Hughes H. Aldosterone and its regulation during diuresis in patients with gross congestive heart failure. *Clin Sci Mol Med* 1974;**47**:301–15.

16 Knight RK, Miall PA, Hawkins LA, Dacombe J, Edwards CRW, Hamer J. Relation of plasma aldosterone concentration to diuretic treatment in patients with severe heart disease. *Br Heart J* 1979;**42**:316–25.

17 Lipkin DP, Poole-Wilson PA. Symptoms limiting exercise in chronic heart failure. *Br Med J* 1986;**292**:1030–1.

18 Cohn JN, Levine TB, Francis GS, Goldsmith S. Neurohumoral control mechanisms in congestive heart failure. *Am Heart J* 1981;**102**:509–14.

19 Cohn JN. Vasodilator therapy for heart failure. The influence of impedance on left ventricular performance. *Circulation* 1973;**48**:5–8.



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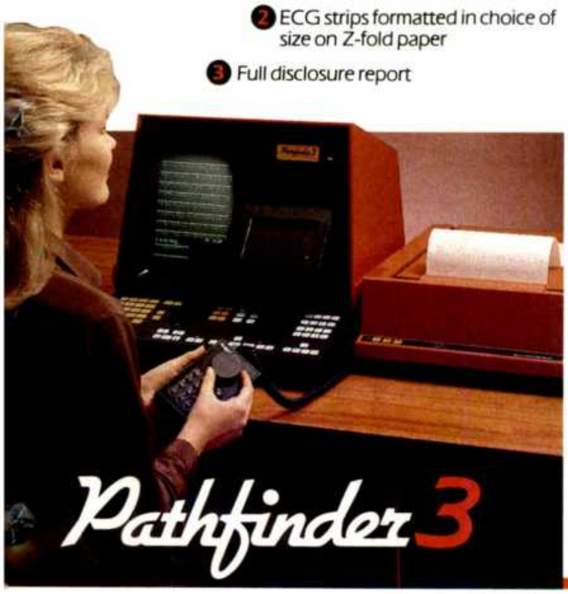

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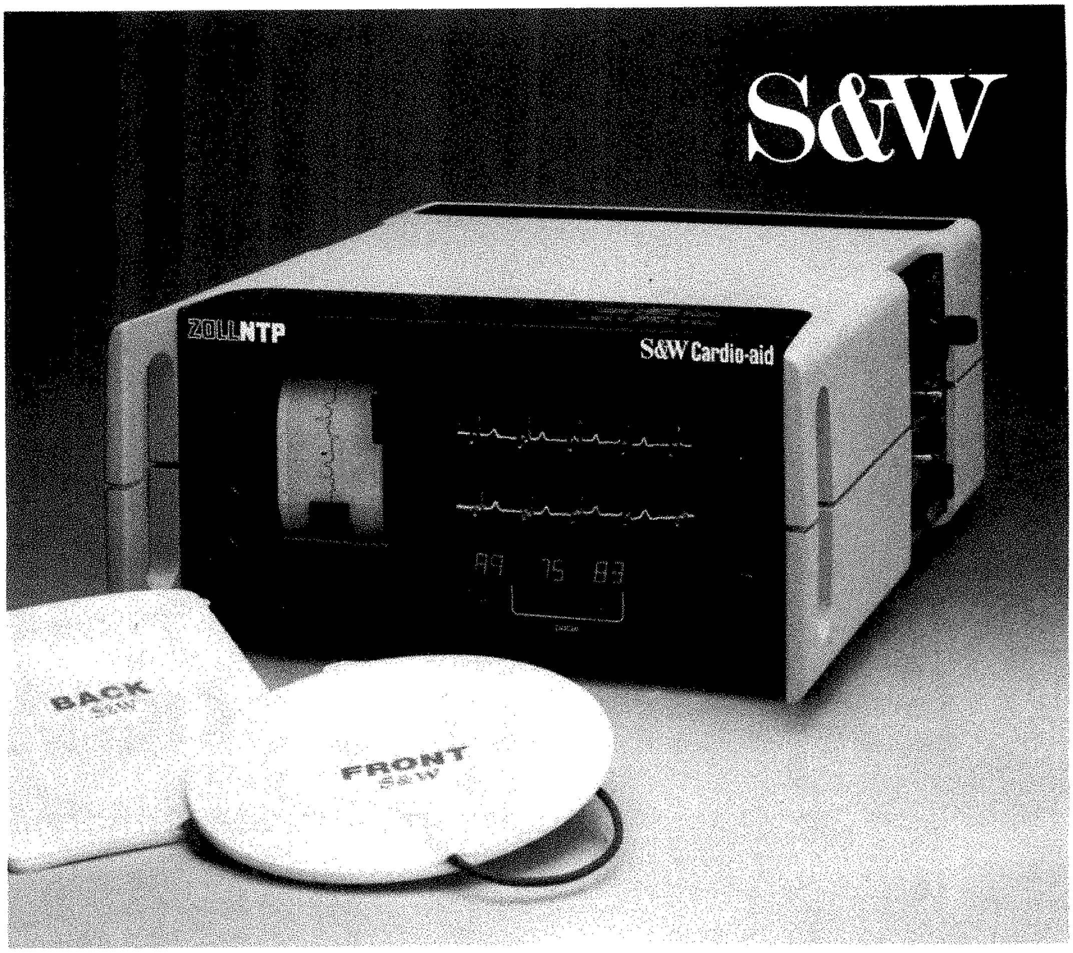

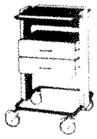
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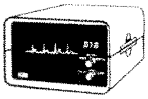
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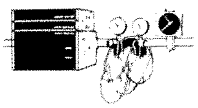
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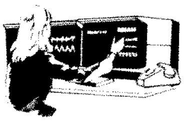
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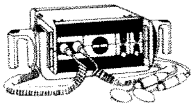
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Br Heart J 1987;57:23–7

The acute inflammatory response to myocardial infarction: imaging with indium-111 labelled autologous neutrophils

D BELL,* M JACKSON,* A M MILLAR,‡ J J NICOLL,† M CONNELL,† A L MUIR*

*From the *Departments of Medicine, †Medical Physics, and ‡Radiopharmacy, Royal Infirmary, Edinburgh*

SUMMARY The uptake of indium-111 labelled neutrophils was examined in 30 patients with acute myocardial infarction by planar imaging and single photon emission computed tomography. The time from venepuncture to reinjection of the autologous labelled neutrophils was $<2\cdot5$ hours and imaging was carried out 24 hours later. Twenty three patients had a positive uptake of neutrophils in the myocardium and imaging was improved by single photon emission computed tomography. There was a significant difference between the intervals from the onset of chest pain to injection of labelled neutrophils between patients with positive and negative images; early reinjection was more likely to produce a positive image. Indeed, all nine patients reinjected within 18 hours of the onset of symptoms had positive images.

The results suggest that the stimulus for activation and migration of neutrophils is transient; this is an important factor if neutrophil release products play a role in cell damage after coronary occlusion.

After myocardial infarction, myocardial cell death and damage produce an acute inflammatory response characterised by the migration of neutrophils into the area of infarcted muscle. Histological examination shows neutrophil infiltration into the infarcted area within 24 hours and the response is maximal at 4–5 days.[1 2] As part of the inflammatory response, neutrophils release oxygen derived free radicals and proteolytic enzymes that in certain circumstances may increase tissue injury. To date, the neutrophil has been implicated in damage to pulmonary capillaries in adult respiratory distress syndrome and may also contribute to the pathogenesis of emphysema. No definite role has been established for the neutrophil extending myocardial damage in man, but in animal models of myocardial infarction, infarct size can be limited by neutrophil inhibition.[3 4]

Although experimental studies have shown uptake of indium-111 (^{111}In) labelled neutrophils in infarcted myocardium[5 6] studies in man have produced conflicting results. McDougall *et al* did not detect uptake of labelled cells in three patients with acute infarction.[7] The time of injection of labelled cells may be of importance, however, because Davies and colleagues obtained positive images when the time to reinjection was short.[8] They also found that positive images were more likely in younger patients.

We have used ^{111}In labelled autologous neutrophils in 24 patients with acute myocardial infarction. Our results confirm the importance of early injection of the neutrophils in obtaining a positive image. We also found that reconstructional imaging from single emission photon computed tomography can be used to resolve difficulties in the interpretation of planar imaging.

Patients and methods

PATIENTS

We studied 30 patients with a diagnosis of acute myocardial infarction based on a history of prolonged ischaemic chest pain (> 30 minutes), electrocardiographic changes associated with myocardial infarction, and a rise in serum creatine kinase to at least twice the upper limit of normal. All gave informed consent, and the study had the approval of

Requests for reprints to Dr D Bell, Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW.

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our institute's ethical committee. Table 1 shows patient details and a full record of the drugs administered within the first 24 hours of myocardial infarction.

PREPARATION OF ^{111}IN LABELLED NEUTROPHILS

Autologous neutrophils were separated from whole venous blood and labelled with ^{111}In-oxine.[9] We used an aseptic technique to withdraw whole blood (60 ml) into a syringe containing 300 units of preservative free heparin. Duplicate samples (25 ml) of blood were layered over 12 ml of mono-poly resolving medium (Flow laboratories) in a sterile tube and centrifuged at 400*g* for 60 minutes. This produced a top plasma layer, two distinct cell bands, and a red cell pellet. We collected 8 ml from the top plasma layer and centrifuged it at 1000*g* for 10 minutes to obtain platelet poor plasma. The remaining plasma and upper cell band were discarded and the neutrophils were recovered from the lower cell band. The neutrophils were washed by diluting the recovered cell suspension to 40 ml with phosphate buffered saline pH 7·4, centrifuging at 400*g* for 10 minutes, and discarding the supernatant. The cell pellet was resuspended in 10 ml phosphate buffered saline and 1 ml of ^{111}In-oxine solution (20–40 MBq) was added drop by drop to the suspension of neutrophils. After incubation at room temperature for 15 minutes, 3 ml platelet poor plasma was added and the cell suspension was centrifuged at 250*g* for 10 minutes. The supernatant was discarded, the neutrophil cell pellet was resuspended to a total volume of 5 ml with equal parts of phosphate buffered saline and platelet poor plasma and the labelled cells were then ready for reinjection.

PATIENT IMAGING

All patients were injected at a fresh site with ^{111}In labelled autologous neutrophils within two and a half hours of the initial venesection. Preliminary studies had suggested that the optimal time for imaging was 24 hours after the injection of labelled neutrophils and we used this imaging time in all our patients. Thus the earliest imaging time for any patient was 36 hours after the onset of chest pain and the latest was 57 hours. Each patient was imaged while supine and planar images were acquired in the anterior, left anterior oblique, and left lateral position for 100 000 counts with a gamma camera (GE400 AT). In 24 patients single photon emission computed tomography was performed with the same gamma camera linked to a DEC PDP11/23+ computer that used locally written software. Ten minutes before the single photon emission computed tomography study, 40 MBq of technetium-99 m (^{99m}Tc) human serum albumin was administered to allow blood pool imaging. A sequence of 64 simultaneous images of ^{99m}Tc and ^{111}In was then acquired as the head of the gamma camera rotated through 180°, starting in the right anterior oblique position. The total imaging time was 32 minutes. At the end of this period computerised reconstruction of the images was performed.

IMAGE INTERPRETATION

An observer who was unaware of electrocardiographic findings or the maximum creatine kinase rise graded planar and single photon emission computed tomography images as positive (in which indium activity was clearly seen in the region of the heart) or negative (where there was no detectable

Table 1 *Patient details and results of imaging with indium-111 labelled autologous neutrophils*

	Positive image (n = 23)	*Negative image (n = 7)*	*Statistical significance*
Age (years)	62·0 (10·8)	59·8 (9·4)	NS (1)
Sex	(6F; 17M)	(2F; 5M)	NS (2)
Location of acute myocardial infarct	10 inf: 13 ant	3 inf: 4 ant	NS (2)
Interval from onset of chest pain to injection of ^{111}In neutrophils (h)	20·3 (6·4)	27·6 (5·8)	$p < 0·02$ (3)
Peak creatine kinase (u/l)	2023·5 (916·0)	1825 (1214·0)	NS (1)
Total leucocyte count (10^9/l)	12·9 (3·2)	12·5 (3·4)	NS (1)
Number of neutrophils injected ($\times 10^8$)	2·7 (0·9)	2·6 (0·7)	NS (1)
Activity of ^{111}In administered (MBq)	32·8 (8·4)	29·4 (8·2)	NS (1)
Drugs administered:			
Non-steroidal anti-inflammatory drugs	5	1	
Lignocaine	2	3	
Calcium antagonists	1	2	
Nitrates	7	1	

All values are shown as mean (SD).
(1) Unpaired *t* test.
(2) Exact probability test.
(3) Unpaired Wilcoxon rank sum test.

activity or where there was an area of activity on planar imaging that was inseparable from the liver, spleen, or ribs). Dual isotope single photon emission computed tomography images were considered to be positive when indium activity was seen in all three reconstruction views and corresponded with the ^{99m}Tc blood pool image.

STATISTICAL ANALYSIS

Data from the groups were compared by means of an unpaired *t* test, exact probability test, or unpaired Wilcoxon rank sum test as appropriate. Values of $p > 0\cdot05$ were regarded as not significant.

Results

In 23 of the 30 patients with acute myocardial infarction there was uptake of ^{111}In labelled neutrophils within the myocardium. Three patterns of cardiac uptake were seen[5]: focal myocardial uptake (12 patients), diffuse myocardial uptake (3 patients), and "doughnut pattern" (3 patients). Figure 1 shows an example of myocardial uptake. Planar images from all patients were graded as unequivocally positive or negative. In six patients in whom the planar images were considered to be negative, single photon emission computed tomography reconstruction showed localised uptake within the myocardium (fig 2). In addition, dual isotope single photon emission computed tomography reconstruction improved anatomical localisation of the infarct by confirming uptake corresponding to the cardiac blood pool (fig 3). There is a significant difference between the intervals from onset of chest pain to injection of labelled neutrophils in the groups with positive and negative images ($p < 0\cdot02$) (table 1). Furthermore, all patients reinjected within 18 hours had positive images whereas positive images were increasingly less common in those injected at progressively later intervals. Other features such as age, sex, peak creatine kinase, peripheral white blood cell count, dose of ^{111}In administered, and drug treatment did not influence the imaging results (table 1).

Discussion

This study confirms that ^{111}In labelled autologous neutrophils can be used to image the inflammatory response to acute myocardial infarction in man. The increased frequency of positive images in this study (77% compared with the 58% as previously described[8]) is in part related to earlier reinjection of ^{111}In labelled neutrophils after the onset of chest pain. This suggests that the stimulus for activation and migration of neutrophils to the area of myocardial damage is transient. This temporal relation may be of particular relevance because of the current interest in reducing the extent of myocardial damage after myocardial ischaemia or infarction by the use of intravenous thrombolytic treatment[10 11] or the potential for the administration of lipoxygenase or cycloxygenase inhibitors.[3]

Thrombolytic treatment can produce coronary reperfusion and hence it could improve myocardial salvage, but it may result in other events which in themselves are potentially harmful.[12] In particular, if the inflammatory response is exaggerated as a

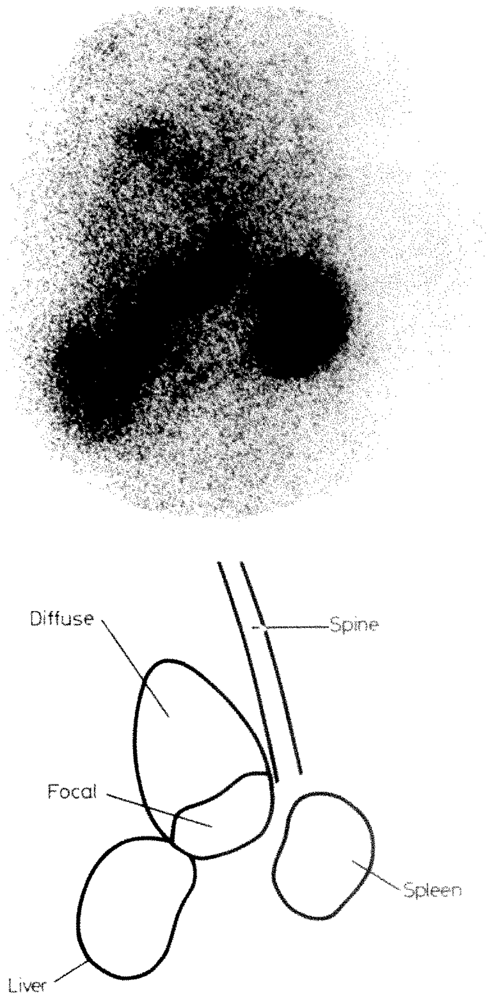

Fig 1 *Planar image in the left anterior oblique view showing normal uptake of ^{111}In labelled neutrophils in the liver and spleen and diffuse uptake in the region of the heart with an area of focal uptake in the inferior wall of the left ventricle. The line drawing shows the areas of uptake.*

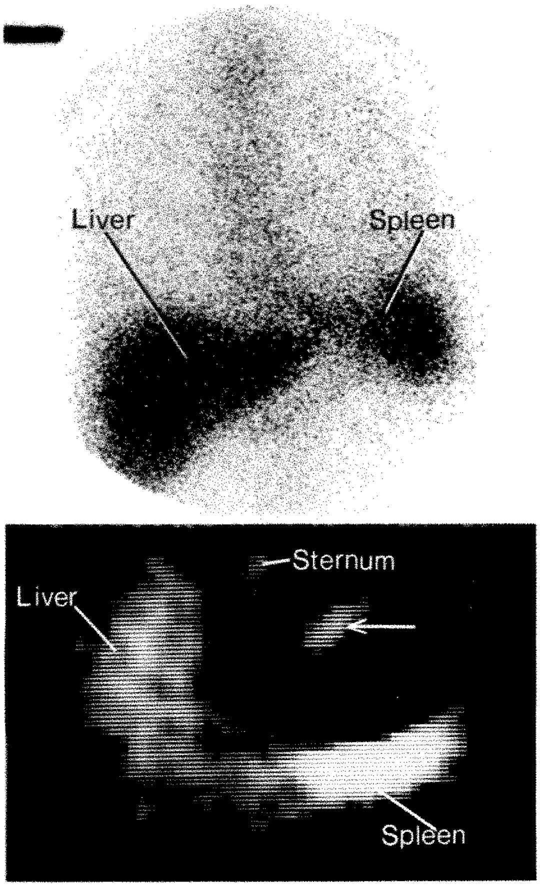

Fig 2 *Anterior planar image with normal uptake in liver and spleen and no definite myocardial uptake (top). Single photon emission computed tomographic image (bottom) in the transverse plane showing uptake within liver and spleen and an area of focal myocardial uptake (arrowed).*

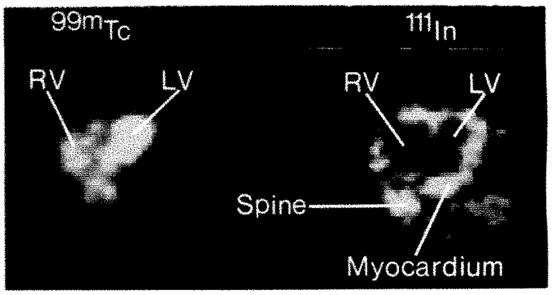

Fig 3 *Simultaneous single photon emission computed tomographic images in the transverse plane. The ^{99m}Tc image shows blood pool in the left and right ventricle. The corresponding ^{111}In image shows extensive uptake within the myocardium of both ventricles.*

result of neutrophils entering ischaemic tissue in greater numbers after reperfusion, the activated neutrophils could generate a number of cytotoxic products including oxygen derived free radicals and proteolytic enzymes, which can extend myocardial damage.[13] Both neutrophil depletion and the use of non-steroidal anti-inflammatory drugs have been shown to reduce infarct size in experimental myocardial infarction,[3 4] and these findings may indicate further potential methods of improving myocardial salvage in the post-infarct period.

Single photon emission computed tomography increased the number of positive images by allowing spatial separation of positive myocardial uptake of indium from adjacent bone, liver, and spleen. It is not possible to ascertain from the planar images whether the ^{111}In activity detected in the region of the heart is due to blood pool activity. Dual isotope single photon emission computed tomography with ^{99m}Tc human serum albumin as a marker of blood pool, however, unequivocally demonstrated that the ^{111}In activity was localised in the myocardium. Single photon emission computed tomography, like pyrophosphate scans,[14] may also provide a method of quantifying neutrophil uptake within the myocardium.

Imaging with ^{111}In labelled autologous neutrophils in patients with acute myocardial infarction allows us to image the acute inflammatory response to myocardial damage, but should not be regarded as a technique for the diagnosis or localisation of acute myocardial infarction because other techniques are currently more successful. If inhibition of neutrophil migration limits the extent of myocardial

Table 2 *Imaging results*

		Positive images		
Time (h)	*Number of patients*	*Planar positive SPECT positive*	*Planar negative SPECT positive*	*Positive images %*
18	9	7	2	100
18–24	12	7	3	83
24–36	9	3	1	44

SPECT, single photon emission computed tomography.

infarction this method can be used to monitor the temporal relation and extent of neutrophil uptake in acute infarction.

References

1 Mallory GK, White PD, Salcedo-Salgar J. The speed of healing of myocardial infarction. *Am Heart J* 1939;18:647–71.

2 Sommers HM, Jennings RB. Experimental acute myocardial infarction. *Lab Invest* 1964;12:1491–503.

3 Romson JL, Hook BG, Rigot VH, Schork MA, Swanson MS, Lucchesi BR. The effect of ibuprofen on accumulation of indium-111-labelled platelets and leukocytes in experimental myocardial infarction. *Circulation* 1982;66:1002–11.

4 Romson JL, Hook BG, Kunkel SL, Abrams GD, Schork MA, Lucchesi BR. Reduction of the extent of ischemic myocardial injury by neutrophil depletion in the dog. *Circulation* 1983;67:1016–23.

5 Weiss ES, Ahmed AD, Thakur ML, Welch MJ, Coleman RE, Sobel BE. Imaging of the inflammatory response in ischemic canine myocardium with ^{111}indium-labelled leukocytes. *Am J Cardiol* 1977;40:195–9.

6 Thakur ML, Gottschalk A, Zaret BL. Imaging experimental myocardial infarction with indium-111-labelled autologous leukocytes: effect of infarct age and residual regional myocardial blood flow. *Circulation* 1979;60:297–305.

7 McDougall IR, Baumert JE, Lantieri RL. Evaluation of ^{111}In leukocyte whole body scanning. *Am J Roentgenol* 1979;133:849–54.

8 Davies RA, Thakur ML, Berger HJ, Wackers FJT, Gottschalk A, Zaret BL. Imaging the inflammatory response to acute myocardial infarction in man using indium-111-labelled autologous leukocytes. *Circulation* 1981;63:826–32.

9 Bell D, Millar AM, McGillivray M, Muir AL. The preparation and in-vivo behaviour of ^{111}In-oxine labelled neutrophils separated from whole blood using mono-poly resolving medium. *Nucl Med Commun* 1986;7:447–53.

10 Mathey DG, Kuck KH, Tilsner V, Krebber HJ, Bleifeld W. Nonsurgical coronary artery recanalization in acute transmural myocardial infarction. *Circulation* 1981;63:489–97.

11 Been M, de Bono DP, Muir AL, Boulton FE, Hillis WS, Hornung R. Coronary thrombolysis with intravenous anisoylated plaminogen-streptokinase complex BRL 26921. *Br Heart J* 1985;53:253–9.

12 Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? *J Clin Invest* 1985;76:1713–9.

13 Werns SW, Shea MJ, Lucchesi BR. Free radicals and myocardial injury: pharmacologic implications. *Circulation* 1986;74:1–5.

14 Jansen DE, Corbett JR, Wolfe CL, *et al.* Quantification of myocardial infarction: a comparison of single photon-emission computed tomography with pyrophosphate to serial plasma MB-creatinine kinase measurements. *Circulation* 1985;72:327–33.

Br Heart J 1987;57:28–31

Fever after acute myocardial infarction in patients treated with intravenous timolol or placebo

CECILIE RISØE, OLE J KIRKEBY, PER GRØTTUM, MAGNUS SEDERHOLM, JOHN K KJEKSHUS

From the Department of Medicine, Baerum Hospital, Baerum, Norway

SUMMARY Body temperature was studied in 65 patients admitted to hospital within four hours of the onset of symptoms of acute myocardial infarction. Thirty three patients had been randomly assigned to intravenous timolol treatment and 32 to placebo treatment. Infarct evolution was assessed by continuous vectorcardiography and creatine kinase release. Maximum and mean temperatures during the first eight days were significantly lower in the timolol group, who were discharged from hospital one day earlier. Eight patients in the placebo group had temperatures of >39° compared with one in the timolol group. Both the mean temperature and the maximum temperature correlated significantly with indices of infarct size and ischaemic area as estimated by cumulative creatine kinase release, QRS vector difference, and ST vector magnitude. The results were consistent with the view that reduction of infarct size may partly explain the reduced pyrexial response after timolol treatment. Other mechanisms are probably also involved in larger infarcts. Because high fever has detrimental haemodynamic effects in acute myocardial infarction, reduction of this response may be beneficial. The results support the early use of β adrenoceptor blockade in acute myocardial infarction.

Fever during acute myocardial infarction is a common finding. Body temperature rises on average more than 1°C.[1] The effect of raised temperatures during infarct evolution has not attracted much attention but may, nevertheless, be clinically important. Fever increases heart rate, cardiac work load, metabolic rate, and overall oxygen consumption. A strong pyrexial response to acute myocardial infarction might therefore be deleterious to the jeopardised myocardium.

In a preliminary study we suggested that treatment with the β adrenoceptor blocker timolol reduces the pyrexial response to acute myocardial infarction.[1] We have confirmed this finding in the present prospective, randomised, double blind, placebo controlled, multicentre study in which timolol or placebo was given intravenously within five hours of the onset of suspected myocardial infarction.[2] Because the study was designed to evaluate the effect of timolol treatment on infarct size we also examined the relation between the increase in body temperature and vectorcardiographic and enzymatic indices of the ischaemic injury.

Patients and methods

Patients of either sex admitted to hospital within four hours of the appearance of symptoms of a first myocardial infarction were considered for inclusion in the study. Exclusion criteria were: bradycardia of <50 beats/min, hypotension (systolic blood pressure <100 mm Hg), rales more than 10 cm above the diaphragm, bronchial obstruction, atrioventricular block of any degree, QRS duration >0·11 second, and concurrent treatment with other cardioactive drugs. The study included 144 patients in nine hospitals who were randomly assigned within each centre to double blind treatment with timolol maleate, given intravenously as two bolus injections of 1 mg, or to an equal volume of saline, followed by a constant infusion of 0·6 mg timolol per hour or matching placebo over 24 hours. Oral treatment (timolol 10 mg twice a day or matching placebo) was given for the remainder of the hospital stay.

Requests for reprints to Dr Cecilie Risøe, Department of Medicine, Baerum Hospital, 1316 Baerum Sykehus, Norway.

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Complete temperature charts were available from four of the participating hospitals (Danderyd, Sweden; Haraldsplass, Rogaland, and Baerum; Norway). Temperatures in all hospitals were measured rectally twice a day (8 am and 4 pm) with standard clinical mercury thermometers. The mean temperature was the average of all temperatures measured (morning and afternoon) during the first eight days. The first temperature value obtained after admission was regarded as the reference value. Patients on antipyretic drugs were excluded from the analyses in this study.

Blood samples for creatine kinase estimation were obtained on admission and at two and four hours and then every four hours for the first 48 hours and thereafter every six hours for up to 72 hours. Creatine kinase was enzymatically assayed with the Merck creatine kinase NAC (N-acetyl-cysteine) kit.[3] The cumulative release of the enzyme was measured according to the method developed by Shell *et al* using an individual decay constant.[4] The creatine kinase release curve was visually inspected without knowledge of the treatment group and at least five points on the downslope were identified for the calculation of the decay constant. In cases with a non-exponential downslope or evidence of repeated enzyme release a standard decay constant of 0·0576 per hour was used.[5] The maximum creatine kinase concentration was defined as the highest value obtained from the cumulative enzyme release curve.

Continuous recording of the Frank orthogonal vectorcardiographic leads was performed for 24 hours on analogue tape and analysed off line without knowledge of the treatment regimen. ST vector magnitude and QRS vector difference were calculated.[2] The first value obtained after admission was regarded as the reference value.

We used the *t* test, analysis of variance, χ^2 test, and Pearson's correlation coefficient to analyse the results.

Results

A total of 76 patients entered the trial from the four hospitals; 40 were randomly assigned to timolol and 36 to placebo. Eleven patients regularly receiving antipyretic drugs were excluded from the temperature study. This left 33 patients in the timolol group (mean (SD) age 65 (12) years) and 32 patients in the placebo group (mean (SD) age 63 (11)). There were 26 men and seven women in the timolol group and 29 men and three women in the placebo group. Three patients in the timolol group and two patients in the placebo group received antibiotics during the early course. The mean body weights in the two groups were similar: 75·3 kg (timolol) and 75·6 kg (placebo).

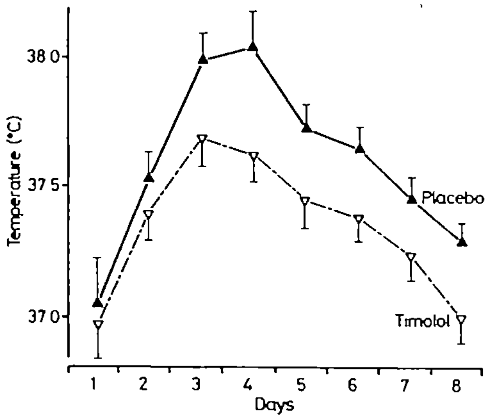

Fig 1 *Mean morning temperature (SEM) after acute myocardial infarction.*

Figure 1 shows the course of the morning temperatures in the timolol and the placebo groups. Temperature rose higher in the placebo group and the fever lasted for on average a day longer than in the timolol group. Morning temperatures remained above 37·3°C for 4·5 days in the timolol group compared with 5·5 days in the placebo group. The difference in temperature was greatest on day 3 ($p < 0{\cdot}05$) and day 4 ($p < 0{\cdot}025$) after the infarction. The curve for evening temperatures lay approximately 0·3°C above the morning temperatures in both groups and the febrile period was one day shorter for timolol treated patients (afternoon temperatures above 37·7°C for four days compared with five days in placebo treated patients). The maximum temperatures reached during the course of acute myocardial infarction were significantly lower in the timolol group than in the placebo group ($p < 0{\cdot}05$). The mean temperature during the first eight days was significantly lower in the timolol group ($p < 0{\cdot}01$). Exclusion of patients treated with antibiotics did not alter the statistically significant differences between the groups. In the timolol group 10 patients had fever >38·5°C during the first eight days; in the placebo group 19 patients had fever above this level ($p < 0{\cdot}025$). Only one patient in the timolol group had fever higher than 39°C, whereas in eight patients in the placebo group this temperature was attained at some time during the first eight days ($p < 0{\cdot}01$).

The mean temperature during the first eight days and the maximal temperature reached were significantly correlated with infarct size and ischaemic area as estimated by cumulative creatine kinase release, maximum QRS vector difference, Table *Pearson's correlation coefficients between body temperature and cumulative creatine kinase release, QRS vector difference, and ST vector magnitude in patients on timolol or placebo*

	Cumulative creatine kinase release	*QRS vector difference*	*ST vector magnitude*
Mean temperature·			
Timolol group	0·20	0·37*	0·30
Placebo group	0·50***	0·49***	0·48***
Both	0·37***	0·49****	0·42****
Maximum temperature·			
Timolol group	0·10	0·38	0·20
Placebo group	0·47***	0·37*	0·37*
Both	0·37***	0·41**	0·33***

*p < 0·05; **p < 0·025; ***p < 0·01; ****p < 0·005.

and initial ST vector magnitude (table). The correlation was highly significant for the total study groups of 65 patients and for the placebo group but not for the timolol group.

Figure 2 shows the mean temperature for patients with a maximum cumulative creatine kinase release < 1000 U/l, 1001 to 2000 U/l, and > 2000 U/l. Timolol reduced the mean temperature in patients with myocardial infarctions associated with a maximum cumulative creatinine kinase release of > 1000 U/l (p < 0·01).

Timolol treated patients were discharged from hospital on average one day before patients on placebo (median hospital stay 11 days in timolol group (range 7–32), 12 days in placebo group (range 8–28)).

Discussion

The present study shows that the early administration of timolol to patients with acute myocardial infarction significantly reduces the pyrexial response to the condition. The fever was reduced both in duration and magnitude and fewer patients on timolol treatment reached high temperatures.

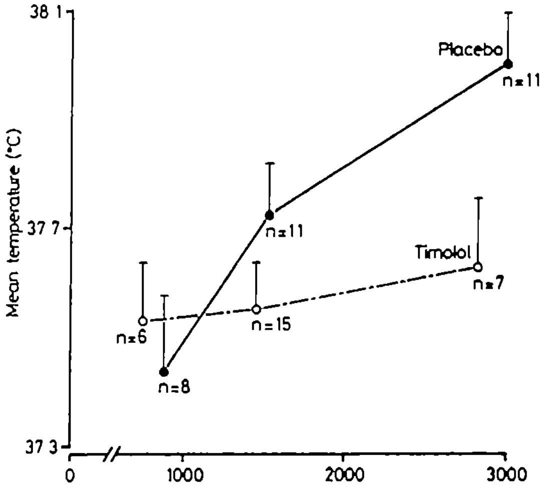

Fig 2 *Mean temperature (SEM) in patients with a maximal cumulative creatine kinase release (CK) below 1000 U/l, 1001 to 2000 U/l, and above 2000 U/l.*

The original study was not designed to estimate differences in temperature between the groups. Temperature is, however, one of the most precise and frequently performed clinical examinations on patients in hospital. The data are thus complete and a prospective trial specifically designed to assess temperature differences in acute myocardial infarction would only be slightly more accurate.

The mechanism of fever in sterile inflammation or trauma such as an acute myocardial infarction is unclear.[6] Fever is generated by an endogenous mediator shown to resemble or be identical to interleukin 1. Interleukin 1 causes fever by altering the set point for the thermostat in the hypothalamus. It is produced by mononuclear phagocytes when they are challenged with viral or bacterial products.[7] Non-infectious diseases such as acute myocardial infarction probably also induce interleukin 1 production as other effects of interleukin 1 (such as a reduction of serum iron, induction of acute phase proteins, and granulocytosis) have been shown to occur in the early phase of the disease.[8] The magnitude of fever, as estimated by mean temperature and maximum temperature during the first eight days, correlated significantly with cumulative creatine kinase release, QRS vector difference, and ST vector magnitude. This suggests that the fever response during acute myocardial infarction is initiated by necrotic myocardium. It is possible that infarcted myocardium induces production of interleukin 1 and that the size and duration of the process of infarction determine the amount of interleukin 1 produced.

Beta adrenoceptor blockade may affect the febrile response after acute myocardial infarction in several ways. As outlined above, infarcted myocardial tissue is a possible stimulus for interleukin 1 production. Our results suggest that the size of the infarction correlates with the pyrexial response. Thus reduction of infarct size may, at least in part, explain the reduced fever response after early timolol treatment. For larger infarctions timolol treatment probably reduces the temperature response through one or more additional mechanisms (fig 2).

The effect of the β adrenoceptors in the temperature regulating centre have not been established. It is possible, at least theoretically, that β blockers may affect temperature regulation through these receptors.[9] Beta adrenoceptors are certainly involved in the peripheral regulation of body temperature. Beta adrenoceptor blockade induces vasoconstriction,[10] which tends to increase body temperature. Reduction of shivering, non-shivering thermogenesis, and metabolic rate, however, lowers body temperature.[10] Our results suggest that the net effect of β adrenoceptor blockage is a reduced pyrexial response.

Fever may impair cardiovascular function. Tachycardia is commonly observed and heart rate is increased by approximately 30% from the basal level at a body temperature of 38·5°C.[11] This increase in heart rate increases myocardial oxygen requirements and might predispose to extension of the infarct and to arrhythmias. Shortening of diastolic perfusion time when heart rate is increased reduces blood flow to the myocardium. Moderate fever reduces stroke volume and cardiac output in patients with a normal myocardium, and subclinical impairment of cardiac function might thus be induced by various febrile conditions.[11–13] Metabolic rate is increased during fever and it has been shown that there is a 13–15% increase in oxygen consumption for every °C increase in body temperature.[14] In acute myocardial infarction an increase of metabolic rate and oxygen consumption increases the risk of cardiac failure. Thus there are several factors to suggest that a strong pyrexial response is detrimental to patients with an acute myocardial infarction.

On average timolol treated patients spent one day less in hospital than placebo treated patients. A similar observation was made in patients with acute myocardial infarction treated with metoprolol.[15] Although the severity of the infarction may be an important determinant for the length of hospital stay, an early return to normal body temperature is usually accompanied by early mobilisation of the patient. Hence the fever reducing effect of timolol might lead to earlier discharge from hospital.

Our results show that timolol reduces the fever after acute myocardial infarction. We believe that this has beneficial haemodynamic effects in these patients and that our results support the early use of β adrenoceptor blockade in acute myocardial infarction.

References

1 Risøe C, Kirkeby OJ. Reduction of the pyrexial response to acute myocardial infarction by beta-adrenoceptor blockade. *Acta Med Scand* 1986; **219**:271–4.

2 The International Collaborative Study group. Reduction of infarct size with the early use of timolol in acute myocardial infarction. *N Engl J Med* 1984;**310**:9–15.

3 The Committee on Enzymes of The Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of creatine kinase in blood. *Scand J Clin Lab Invest* 1976;**36**·711–23.

4 Shell WE, Kjekshus JK, Sobel BE. Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity. *J Clin Invest* 1971;**50**:2614–25.

5 Sederholm M, Grøttum P, Erhardt L, Kjekshus JK. Quantitative assessment of myocardial ischaemia and necrosis by continuous vectorcardiography and measurement of creatine kinase release in patients. *Circulation* 1983;**68**:1006–12.

6 Atkins E. Fever—new perspectives on an old phenomenon. *N Engl J Med* 1983,**308**:958–60

7 Baracos V, Rodeman HP, Dinarello CA, Goldberg AI. Stimulation of muscle protein degradation and prostaglandin E2 release by leucocytic pyrogen (Interleukin 1). *N Engl J Med* 1983;**308**:553–8

8 Fitzsimons EJ, Kaplan K. Rapid drop in serum iron concentration in myocardial infarction. *Am J Clin Pathol* 1980;**73**:552–5

9 Kasiazek A, Klemok Z. The central action of beta-adrenergic receptor blocking drugs. *Pol J Pharmacol Pharm* 1974;**26**:287–95.

10 Welle SL, Thompson DA, Campbell RG. Beta-adrenergic blockade inhibits thermogenesis and lipolysis during glucoprivation in humans. *Am J Physiol* 1982;**243**·R379–82.

11 Abdullah AK, Goel JK, Siddiqui MA. Systolic time intervals in febrile states. *Jpn Heart J* 1981; **22**·739–45.

12 Friman G, Wright JE, Ilback NG, *et al.* Does fever or myalgia indicate reduced physical performance capacity in viral infections? *Acta Med Scand* 1985;**217**·353–61.

13 Friman G. Effects of acute infectious diseases on circulatory function. *Acta Med Scand* 1976;**200** (suppl 592):1–62.

14 duBois EF The basal metabolism in fever. *JAMA* 1921;**77**:352–5.

15 Herlitz J, Hartford M, Pennert K, *et al.* Goteborg metoprolol trial: clinical observations *Am J Cardiol* 1984;**53**:37D–45D.

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Relation of human cardiac action potential duration to the interval between beats: implications for the validity of rate corrected QT interval (QTc)

W A SEED, M I M NOBLE, P OLDERSHAW, R B WANLESS, A J DRAKE-HOLLAND, D REDWOOD, S PUGH, C MILLS

From the Department of Medicine, Charing Cross and Westminster Hospital Medical School, London; King Edward VII Hospital, Midhurst, West Sussex; Department of Cardiology, Brompton Hospital, London; Department of Cardiology, Cardiothoracic Institute, London and Midhurst, West Sussex; and Departments of Medicine 1 and Cardiology, St George's Hospital Medical School, London

SUMMARY Fourteen patients undergoing routine cardiac catheterisation were paced at a steady frequency; after this test, stimuli were introduced with a variable preceding interval (test pulse interval). The QT interval of the electrocardiogram and the duration of the monophasic action potential of the right ventricle were measured. QT interval is a function of action potential duration; the two variables were very closely correlated in this study. Both these variables increased in duration with increasing test pulse interval. A biphasic response, as previously reported, was not seen. An increase in steady state pacing frequency caused QT interval and action potential duration to decrease for any given R-R interval. When frequency of stimulation was suddenly increased and then maintained, there was an immediate action potential shortening followed by a further more gradual shortening occurring over several minutes. These results imply that a simple correction of QT interval for heart rate (QTc) is inadequate.

It is concluded that the relation between action potential duration (or QT interval) and heart rate depends on both the instantaneous interval between beats and the duration of the prevailing heart rate.

When the heart is electrically activated, depolarisation of the myocardium is registered as an upstroke of the action potential and as the QRS complex of the surface electrocardiogram. The period of myocardial depolarisation is indicated by the plateau of the action potential; this is terminated by repolarisation—that is the downstroke of the action potential and the T wave of the electrocardiogram. The interval from the QRS to the T wave of the electrocardiogram (QT interval) thus reflects the duration of the action potential. We have investigated the effect of heart rate on the QT interval using the more direct and accurate measurement of ventricular action potential duration. When an electrical impulse is delivered to the heart immediately after an action potential, the membrane is refractory and no response is obtained. When the stimulus is delivered a little later, action potentials are obtained which (in most species) are shorter than those in the preceding steady state; they become longer as the interval between beats is increased. When this relation is explored formally by pacing at a given steady state frequency and by introducing a test pulse interval at progressively increasing intervals[1 2] a relation can be defined between action potential duration (or QT interval) and test pulse interval (R-R interval), which is termed the electrical restitution curve.[3–6] There is one study in man that included only five patients, two of whom showed prolongation of the action potential duration over a range of R-R intervals of 300–400 ms.[6] This is unlike the findings in animals of Boyett and Jewell[4] and Elzinga *et al.*[5] The first objective in the present study was to examine electrical restitution in

Requests for reprints to Dr M I M Noble, King Edward VII Hospital, Midhurst, West Sussex GU29 0BL.

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a larger group of patients in order to establish the correct restitution curve.

Electrical restitution does not explain all the changes in action potential (and QT interval) that take place when the heart rate is increased. A sustained increase in heart rate causes a slow progressive shortening of QT interval and action potential duration over a period of several minutes. This has been shown for the guinea pig by Attwell *et al*[7] and for intact dog by Drake *et al.*[8] Attwell *et al* also showed that changes in human QT interval (which corresponds to the action potential duration) followed a similar pattern.[7] The second objective of the present study was to examine the longer term response of action potential duration to an increase in heart rate. This is of considerable importance in understanding the relation of QT interval to cardiac frequency.[9-11] Bazett's correction of the QT interval (QTc) was formulated to allow for physiological variation in heart rate, assuming a linear relation. The results of Attwell *et al*[7] strongly suggest that such correction is invalid and we therefore wished to confirm or deny that suggestion with a definitive study.

Patients and methods

PATIENTS

Fourteen patients were studied (9 men and 5 women, aged 36–74 years (table 1)). They were patients with ischaemic heart disease who were routinely undergoing cardiac catheterisation for diagnostic purposes. All drugs were stopped 24 hours before the study. No patients had received amiodarone before or during the study. The patients were given 100 mg atenolol orally 4 hours before the study, to avoid the complication of variable adrenergic status, and diazepam 10 mg orally an hour before the study. Measurements were made during quiet breathing. The study was approved by the ethics committee of the participating hospitals. Informed consent was obtained from each patient before the study.

Table 1 *Patient data and steady state intervals used in the study*

Patient No	*Sex*	*Age*	*Steady state interval (ms)*
1	M	73	800
2	F	72	800
3	M	60	800
4	M	61	800
5	M	49	800
6	M	58	600
7	M	38	500
8	F	74	500 and 800
9	M	36	600
10	F	52	500
11	F	51	500 and 700
12	M	58	450 and 750
13	M	71	800
14	F	57	500 and 800

MEASUREMENTS

Endocardial action potentials

An action potential catheter as modified by Miller *et al*[12] was used. The catheter was passed from the right femoral vein to the right ventricle and was allowed to touch the endocardial surface. A site on the septum towards the middle of the ventricle was chosen whenever possible to minimise variability between action potential duration and the QT interval. The potential difference between the two silver-silver chloride electrodes of the catheter was measured with a DC amplifier and an oscillographic or electrostatic recorder. Recordings were made simultaneously on to a Racal instrumentation tape recorder. The duration of the action potentials (expressed as time during which the myocardial cells were depolarised by more than 70%) was measured manually from all records at a fast paper speed. A standard electrocardiogram was monitored throughout the procedure. When we analysed the action potential duration we always checked the electrocardiographic signal to ensure that there were no spontaneous beats. QT interval was measured simultaneously from the standard electrocardiogram.

Pacing

The heart was stimulated by a right atrial (3 patients) or right ventricular (11 patients) bipolar pacing catheter introduced from the right femoral vein. If the atrioventricular node became refractory during attempted atrial pacing, ventricular pacing was substituted. Stimuli of 2 ms duration and twice threshold strength were produced from an isolated constant current source (Devices 2533) which was triggered by a programmable stimulator.

Pacing protocols

To determine the electrical restitution curves, the hearts were paced at a constant base cycle length (see table 1 for details) until action potential duration had reached a steady state. This was usually in 2–3 minutes. In the first five studies we used a basic pacing interval of 800 ms (table 1). This was chosen because it was expected to be comfortably shorter than the spontaneous R-R interval of patients on β adrenergic blockade. We then wished to check the effect of higher basic pacing frequency and used intervals of 500 or 600 ms (patients 6, 7, 9, and 10; table 1). We were also able to study two basic frequencies in individual patients (patients 8, 11, 12, and 14; table 1). After each period of steady pacing at these intervals a test stimulus was applied after the refractory period of the last regularly paced response via the programmable stimulator. After each test stimulus, regular pacing at the basic cycle length was resumed for at least ten beats to allow recovery of the original steady state. Test pulse intervals were applied with either a progressively longer or shorter interval in sequence, in each patient. Action potential durations were measured at 70% repolarisation and plotted against test cycle length. For pooled data, the duration of the action potential in response to the test beats was expressed as a percentage of that of the steady state beats. When a frequency switch of steady state interval was made (patients 8, 11, 12, and 14) the time taken for the response to reach a new steady state was carefully monitored.

Results

The monophasic action potential signals recorded with the electrode catheter were of good quality for determination of action potential duration (fig 1). As the interval preceding a test stimulus was extended, the duration of the action potential also increased—see the electrical restitution curve (fig 2a). The results in the three patients in whom the protocol could be carried out by atrial pacing without atrioventricular conduction problems were similar to those in the 11 patients studied by right ventricular pacing. We have averaged the data for all those studies in which the steady state interval was 800 ms (fig 2b). This data does not include some patients in whom the spontaneous rate was too high to allow steady pacing at 800 ms intervals. The electrical restitution curves in these patients were similar, however. In every patient there was a smooth increase in action potential duration with interval over the whole range studied. A transient decrease at intermediate intervals, as seen in two patients of Franz *et al*,[6] was not seen in any of the present patients studied.

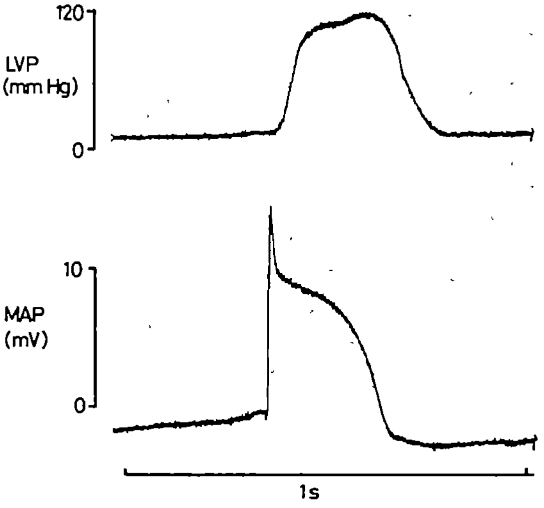

Fig 1 *Recordings of typical monophasic action potential signal (MAP) from the human heart and left ventricular pressure (LVP).*

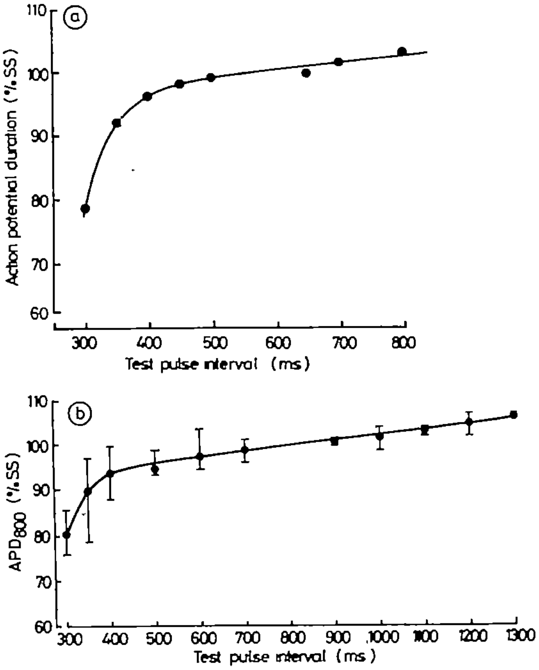

Fig 2 *Electrical restitution curves in which action potential duration of the test beats as a percentage of steady state control action potential duration is plotted as a function of test pulse interval. (a) A typical individual example; (b) mean results (range) for all patients in whom the steady state interval was 800 ms.*

In four patients we also studied the electrical restitution curve at a higher steady state frequency. This intervention was not possible in some patients because of the occurrence of angina or because it was not advisable to prolong the study. In the cases where results at two frequencies were obtained, the action potentials for all test pulse intervals were shortened at the higher frequency; this resulted in a downward shift of the electrical restitution curve (fig 3). Table 2 summarises the data from all patients.

Figure 4 illustrates the effects of a sudden switch in frequency of stimulation. On the first beat at the high frequency, the action potential was shortened to a degree that was consonant with the electrical restitution curve for the control (low) frequency.

Table 2 *Action potential duration measurements for the individual test pulse intervals used in the study*

Patient No	Interval 300	350	400	450	500	550	600	700	800	900	1000	1100	1200	1300	1400	1500	1600
1	—	235	268	275	280	283	289	280	280	277	284	282	—	—	—	—	—
2	256	287	301	—	292	—	299	300	—	302	312	310	320	—	—	—	—
3	—	—	—	260	255	270	288	297	309	300	308	312	313	318	—	—	—
4	199	246	248	—	242	—	253	265	—	256	259	254	267	—	—	—	—
5	194	—	233	—	237	—	244	252	—	250	250	260	—	—	—	—	—
6	209	242	255	258	259	262	263	266	—	—	—	—	—	—	—	—	—
7	—	—	230	230	—	250	260	260	265	280	280	285	300	300	300	—	—
8a	—	—	203	207	—	216	221	228	232	239	244	248	252	253	254	260	270
b	—	—	—	257	256	260	262	270	275	282	289	290	297	302	302	305	268
9	—	—	—	192	200	202	206	218	222	—	—	—	—	—	—	—	—
10	255	276	276	—	276	—	300	—	—	—	—	—	—	—	—	—	—
11a	206	218	218	222	—	—	210	206	210	—	—	—	—	—	—	—	—
b	213	242	242	254	270	—	—	280	280	280	276	—	—	—	—	—	—
12a	200	203	207	—	213	213	218	217	223	223	228	228	237	—	—	—	—
b	211	234	247	248	—	—	—	257	—	—	270	—	—	—	—	—	—
13	—	265	290	293	305	300	303	310	321	333	325	—	350	—	—	—	—
14a	—	235	237	237	235	—	237	250	258	269	295	—	—	—	—	—	—
b	—	—	—	222	230	—	238	244	247	251	249	258	256	—	—	—	—

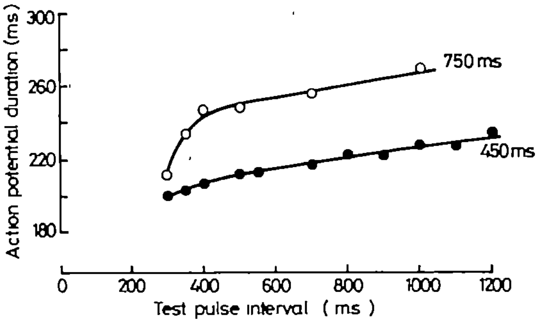

Fig 3 *Two electrical restitution curves in one patient recorded at two different steady state intervals.*

This was followed by a progressive further shortening for subsequent beats at the new (high) frequency. This shortening continued over several minutes (fig 4); even after three minutes there was still a trend to further action potential shortening with time. In all four cases the changes were qualitatively similar to those described for one patient by Franz *et al.*[13]

In those patients in whom adequate comparison could be made between action potential duration and simultaneous QT interval, the Spearman Rank correlation coefficient ranged from 0·80 to 0·88. Most of the scatter contributing to the comparative analysis was derived from the QT measurements.

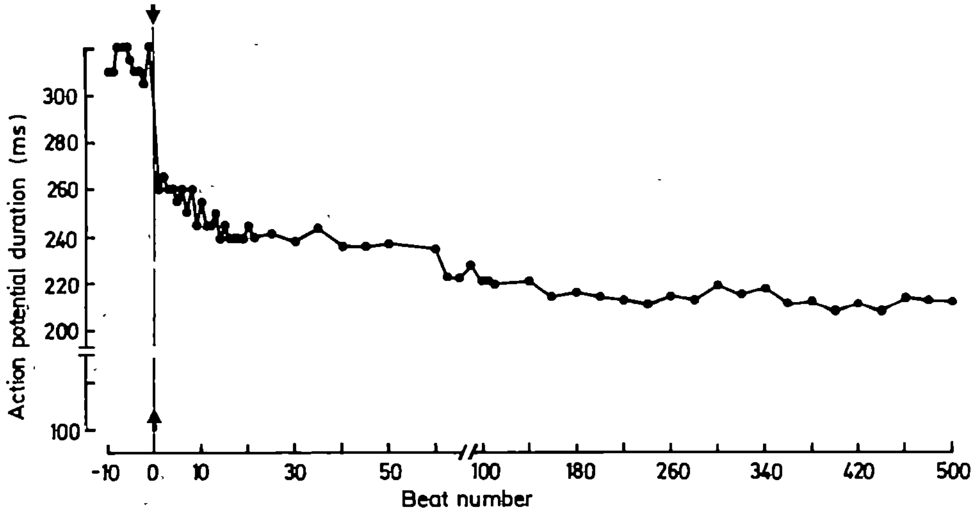

Fig 4 *Beat to beat values for action potential duration after a sudden change of interval from 750 to 450 ms.*

Discussion

Our results confirm that in the intact human heart the relation between action potential duration (and QT interval) and the R-R interval is similar to that of isolated cardiac muscle[3 4 14 15] and intact dog.[5] This relation between action potential duration and test pulse interval is referred to as the electrical restitution curve.[4 5]

A previous report suggests that the electrical restitution curve of man was of a different form, namely a biphasic relation[6] similar to that of the rabbit.[16] There are species differences in the shape of electrical restitution curves. The shapes of the electrical restitution curves reported for two of the five patients by Franz *et al*[6] resemble those of the rabbit, in that action potential duration at intervals of 300–400 ms was prolonged. Action potential duration then declined again at frequencies between 400 and 500 ms, before increasing again with longer intervals. We did not observe such changes in any of our 14 patients. In the study of Franz *et al* the prolonged action potentials at short preceding intervals were accompanied by changes in the shape of the action potential waveform.[6] We are of the opinion that monophasic signals do not give reliable information on action potential shape but only of action potential duration.[17] We would therefore place more reliance on the present measurements in a considerably larger group of patients, and we conclude that the human electrical restitution curve is very similar to that of the cat[4] and of the dog.[5]

The electrical restitution curve determines the action potential duration and QT interval of only the first excitation after the first short R-R interval. If short R-R intervals are maintained by a continuation of pacing at a high frequency there is a further progressive shortening of the action potential duration and QT interval over a period of several minutes. This was reported for the QT interval of man by Attwell *et al*[7] and for the action potential duration of one person.[13] If the electrical restitution curve is redefined after such a period, it is found to show shorter action potential duration at all R-R intervals. This downward shift of the electrical restitution curve when the steady state frequency is higher (fig 3) is very similar to the findings in the dog.[5] The changes in action potential duration with a maintained frequency increase after a sudden switch (fig 4) are also very similar to findings in the dog for both Purkinje fibres[18] and endomyocardial recordings in the intact animal.[8]

It would seem reasonable therefore to assume that the changes we see are due to mechanisms that apply generally in higher animals. The immediate action potential shortening on the first beat is a shift along the restitution curve for the low steady state frequency. The restitution curve depends on changes in factors affecting recovery of the cell membrane after a depolarisation. This is thought to be due in part to recovery from inactivation of the slow inward calcium channels.[18] There is also decay of outward potassium currents during the polarised period (or electrical diastolic interval)[6] which may be interrupted by shorter intervals. The mechanisms underlying the second, slower phase of further action potential shortening during a period of high frequency pacing (fig 4) were examined in some detail in the intact dog by Drake *et al.*[8] The slow time course of change in action potential duration after an increase in stimulation frequency suggested that these changes are caused by the accumulation of an ion or metabolite, or possibly by changes in activity of the electrogenic Na^+-K^+ pump[18]; such mechanisms appear to act via an increase in outward background current.[18] Whatever mechanism is responsible for this change, it is clearly maintained for at least 1400 ms.

The results of our study are relevant to arguments concerned with the corrections to be made to QT interval to allow for heart rate.[19–21] Thus from our results and from those using QT intervals[7] it must be concluded that the relation between heart rate and QT interval is not constant. For instantaneous differences in interval between beats, QT interval must be governed by the electrical restitution curve (fig 1). For more prolonged periods, the relation will also be affected by the slower changes in action potential duration, which are time dependent (fig 4). We have confirmed that after one beat at a different interval, it takes up to 10 beats for a steady state to be regained. When there is a switch from one sustained period at a given frequency to a new frequency, it takes at least three minutes for a new steady state to be reached.

Our study does not explore the additional influence of the sympathetic nervous system upon action potential duration and QT interval, because our patients were deliberately subjected to β adrenergic blockade by atenolol. An increase in sympathetic activity in the absence of such blockade causes a further shortening of action potential duration at a given fixed heart rate[22]; this effect is valuable in producing an increase in heart rate with exercise in appropriately programmed pacemakers.[22] Any correction of QT interval for heart rate that ignores changes that might have occurred during the preceding five minutes must therefore be unreliable. Such dubious corrections are sometimes used in human clinical pharmacological studies—for example class III antiarrhythmic agents. From our study we conclude that the use of rate corrected QT interval is not valid. We suggest that such studies should be carried out at constant heart rate achieved by pacing for at least three minutes.

References

1 Pidgeon J, Lab MJ, Seed WA, Elzinga G, Papadoyannis D, Noble MIM. The contractile state of cat and dog heart in relation to stimulation frequency. *Circ Res* 1980;**47**:559–67.

2 Pidgeon J, Miller GAH, Noble MIM, Papadoyannis D, Seed WA The relationship between the strength of the human heart beat and the interval between beats. *Circulation* 1982;**65**:1404–10.

3 Bass BG. Restitution of the action potential in cat papillary muscle. *Am J Physiol* 1975;**228**:1717–24.

4 Boyett MR, Jewell BR. A study of the factors responsible for rate-dependent shortening of the action potential in mammalian ventricular muscles. *J Physiol (Lond)* 1978;**285**:359–80.

5 Elzinga G, Lab MJ, Noble MIM, *et al.* The action potential duration and contractile response of the intact heart related to the preceding interval and the preceding beat in the dog and cat. *J Physiol (Lond)* 1981;**313**:481–500.

6 Franz MR, Schaefer J, Schoettler M, Seed WA, Noble MIM. Electrical and mechanical restitution of the human heart at different rates of stimulation. *Circ Res* 1983;**53**·815–22.

7 Attwell D, Cohen I, Eisner DA. The effect of heart rate on the action potential of guinea-pig and human ventricular muscle. *J Physiol (Lond)* 1981;**313**:439–61.

8 Drake AJ, Noble MIM, Schouten V, Seed WA, ter Keurs HEDJ Wohlfart B. Is action potential of the intact dog heart related to contractility or stimulus rate? *J Physiol (Lond)* 1982;**331**:499–510

9 Bazett HC. An analysis of the time relations of the electrocardiograms. *Heart* 1920;**7**:353–69.

10 Shipley RA, Hallaran WR. The four-lead electrocardiogram in two hundred normal men and women. *Am Heart J* 1936;**11**:325–45

11 Lepeschkin E. *Modern electrocardiography*, vol. 1. Baltimore: Williams and Wilkins, 1951.

12 Miller GAH, Noble MIM, Papadoyannis D, Pidgeon J, Seed WA. A catheter-tip method for recording monophasic action potentials from the canine or human endomyocardium. *J Physiol (Lond)* 1980; **305**:7–8P.

13 Franz M, Schoettler M, Schaefer J, Seed WA. Simultaneous recording of monophasic action potentials and contractile force from the human heart *Klin Wochenschr* 1980;**58**:1357–9.

14 Hauswirth O, Noble D, Tsien RW. The dependence of plateau currents in cardiac Purkinje fibres on the interval between action potentials *J Physiol (Lond)* 1972;**222**:27–9.

15 Gettes LS, Reuter H. Slow recovery from inactivation of inward currents in mammalian myocardial fibres. *J Physiol (Lond)* 1974;**240**:703–24.

16 Wohlfart B. Relationships between peak force, action potential duration and stimulus interval in rabbit myocardium. *Acta Physiol Scand* 1979;**106**:395–409.

17 Hoffman BF, Cranefield PF, Lepeschkin E, Surawicz B, Herrlich HC. Comparison of cardiac monophasic action potentials recorded by intracellular and suction electrodes. *Am J Physiol* 1959;**196**:1297–301.

18 Boyett MR, Fedida D. Changes in the electrical activity of dog cardiac purkinje fibres at high heart rates. *J Physiol (Lond)* 1984;**350**:361–91.

19 Kelman AW, Whiting B, Sumner DJ. Correction equation for ECG time intervals. *Br J Clin Pharmacol* 1984;**18**:113–4.

20 Staniforth DH. The QT interval and cycle length. the influence of atropine, hyoscine and exercise. *Br J Clin Pharmacol* 1983;**16**:615–21.

21 Evans SJW, Kelman AW, Whiting B, Sumner DJ, Staniforth DH. Correction equation for ECG time intervals; correction equation for QT interval [Correspondence]. *Br J Clin Pharmacol* 1985;**19**. 860–2.

22 Rickards AF, Norman J. Relation between QT interval and heart rate: new design of physiologically adaptive cardiac pacemaker. *Br Heart J* 1981;**45**·56–61.

Br Heart J 1987;57:38–43

Doppler ultrasound in the assessment of severity of coarctation of the aorta and interruption of the aortic arch

A B HOUSTON, I A SIMPSON, J C S POLLOCK, M P G JAMIESON, W B DOIG, E N COLEMAN

From the Departments of Cardiology and Cardiac Surgery and University Department of Child Health, Royal Hospital for Sick Children, Glasgow

SUMMARY Doppler ultrasound was used to investigate 48 infants and children (age 2 days–16 years, weight 1·0–58 kg) with aortic arch abnormalities. In only 38 of the 42 with an important coarctation was an increased blood flow velocity from the distal arch demonstrated. In three with interruption of the aortic arch an increased velocity recorded from the region of the distal arch was thought to represent ductal flow. There was little difference between the peak to peak and instantaneous maximum gradients in the 20 patients with important coarctation in whom direct pressure measurements both proximal and distal to the obstruction were made at catheterisation. There were poor agreements between Doppler and measured peak to peak and instantaneous gradients in the 17 patients found to have both an increased velocity and important coarctation.

It is concluded that although an increased blood flow velocity in the distal arch is usually demonstrated in coarctation this may not occur with severe obstruction. Furthermore, the maximum velocity is not related to the anatomical severity of the obstruction and the Doppler estimate of pressure drop in coarctation may not even reliably predict that measured at catheterisation.

The diagnosis of coarctation of the aorta is usually based on clinical examination, and further investigations are directed at defining its site and nature to permit the correct surgical approach. Although echocardiography often provides this information and allows surgery to be undertaken safely without catheterisation, another non-invasive diagnostic technique would be useful in patients in whom a clear echocardiographic image of the coarctation site is not obtained.

Reports have suggested that in some instances Doppler ultrasound provides such a technique by demonstrating increased flow velocity in the descending aorta[1–3] and that it can also give accurate information on the gradient across the obstruction.[2] These studies did not measure gradient by invasive means and since our experience has indicated some problems in the application of Doppler ultrasound in this condition, it seemed appropriate to report our findings. Furthermore, previous reports have only briefly considered the different wave form patterns[1] that are obtained from patients with coarctation.

Patients and methods

We studied 48 patients (14 neonates, nine older infants, and 25 children) aged 2 days–16 years (mean 3 years 6 months) and weighing 1·0 to 58 kg (mean 13·8 kg). In three patients who had undergone coarctation repair the narrowing was minimal on angiocardiography and surgery was not considered necessary. The exact diagnosis was ascertained at surgery in all the others; previous catheterisation had been performed in all but 13 (eight neonates, three older infants, and two children). Of the 23 infants, 18 had preductal coarctation (14 with a ductus arteriosus), two had postductal coarctation, and three had interrupted aortic arch with a ductus arteriosus. Ten patients (including one infant) had already undergone coarctation repair. The table

Requests for reprints to Dr A B Houston, Royal Hospital for Sick Children, Yorkhill, Glasgow G3 8SJ

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Table *Summary of the more important clinical and diagnostic features in the different age groups*

Diagnosis and age	*Total No*	*DA present*	*Catheterisation undertaken*	*DA and catheter*	*Previous operation*	*Arch velocity* $>2{\cdot}2$ *m/s*
Coarctation <1 month	11	9	4	3	0	11
Coarctation 1–12 months	9	5	6	2	1	8
Coarctation >1 year	22	1	20	1	6	19
Interruption (all <1 month)	3	3	2	2	0	3
Insignificant obstruction	3	0	3	0	3	2

DA, ductus arteriosus.

summarises the age groupings, investigation, and findings.

At catheterisation the pressure was measured directly through a fluid filled system both proximal and distal to the obstruction in 23. Pressures on both sides of the obstruction were measured simultaneously in 12; the proximal measurement was made with a catheter in the left ventricle (9) or the aortic arch through the coarctation (3) and the distal one through a needle in the femoral artery or the side arm of a sheath in the iliac artery. In the remaining 11 patients pressures were measured by catheter withdrawal across the coarctation and tracings distal to the coarctation were superimposed on proximal ones to simulate simultaneous pressure measurements; to minimise error, beats with almost equal R–R intervals were chosen. The peak to peak and maximum instantaneous pressure differences were measured from each tracing. Catheterisation was undertaken in seven infants with a ductus arteriosus, with pressures being measured in both the pulmonary artery and descending aorta in five.

The Doppler investigations were performed by means of a 2 MHz probe with a continuous and pulsed wave system (Alfred, Vingmed) and a spectrum analyser (Doptek). After echocardiographic examination a routine Doppler study was performed, the suprasternal or left upper parasternal positions being used to obtain the optimal signal of flow through the aortic arch and coarctation site. From the Doppler signals from the ascending aorta and aortic arch the maximum velocity of blood flow in m/s (V) was measured and the modified Bernoulli equation ($\Delta P = 4V^2$)[4] was used to convert this into Doppler estimate of gradient in mm Hg (P). We then compared the Doppler measurement of flow velocity in the ascending and descending aorta and the maximum Doppler gradient in the descending aorta with the measured maximum instantaneous and peak to peak gradients over the coarctation. In those infants with a preductal coarctation and a ductus arteriosus or arch interruption who underwent catheterisation we also compared the Doppler findings with the gradient from the main pulmonary artery to the descending aorta. In one patient the Doppler study was performed while a balloon catheter was inflated within the ductus.

In the normal individual forward flow in both the ascending and descending aorta is of approximately the same velocity,[5] that is < 2·0 m/s and is usually confined to systole. The wave forms from the distal arch in many of those with coarctation, however, demonstrated continuing forward flow in diastole. The Doppler wave forms were reviewed to assess the timing of forward flow paying particular attention to diastolic flow patterns and determining whether there was no diastolic flow or early diastolic flow only or pandiastolic flow.

Results

INFANTS WITH COARCTATION

Maximum velocities in the ascending aorta were <2·2 m/s (20 mm Hg) in 19 of the 20 infants, the other having an increased velocity related to the presence of associated aortic stenosis. Doppler echocardiography demonstrated a velocity, apparently from the distal arch, indicating flow away from the transducer of >2·4 m/s (equivalent to a gradient of 23 mm Hg) in 19 of the 20 infants (fig 1); Doppler gradients ranged from 23 to 80 mm Hg with a mean of 38 mm Hg. No increased velocity was found in the remaining 6 month old infant with a narrow isthmus and a web proximal to a 4 mm ductus; catheterisation was not performed but blood pressure measurements showed the leg pressure to be 30 mm less than that in the arm.

In one neonate in whom Doppler echocardiography had recorded increased velocity of flow away from the transducer (2·85 m/s, equivalent to a gradient of 33 mm Hg) catheterisation while prostaglandin E2 was being infused showed a tight coarctation and a ductus arteriosus with a measured drop from main pulmonary artery to aorta of 31 mm Hg. The Doppler signal disappeared when a balloon was inflated in the ductus arteriosus; it reappeared when the balloon was deflated, which suggests that this flow was ductal and not through the coarctation.

The gradient from the main pulmonary artery to the descending aorta was measured at cath-

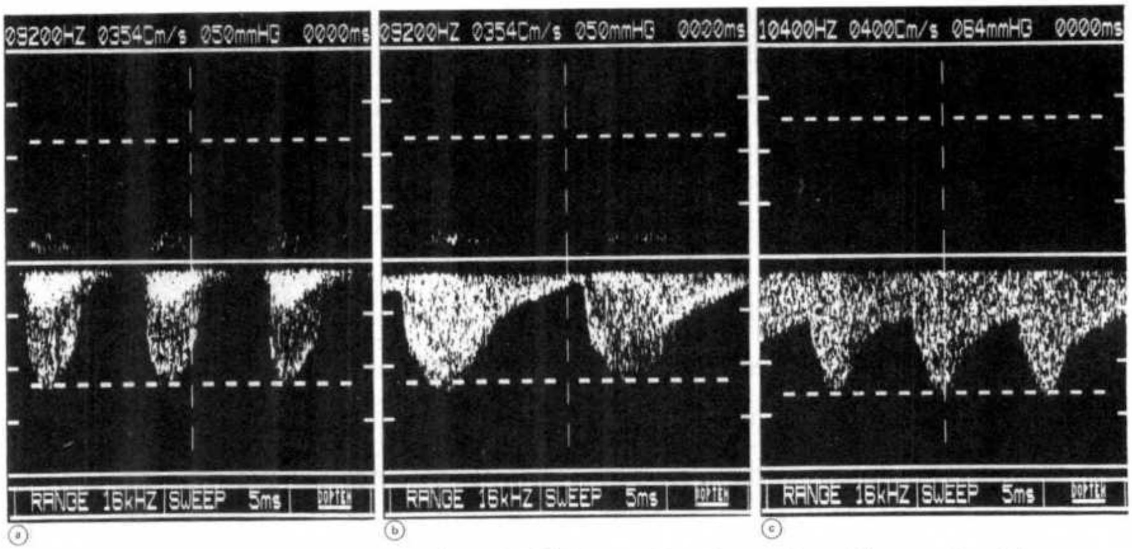
09200HZ 0354Cm/s 050mmHG 0000ms
09200HZ 0354Cm/s 050mmHG 0000ms
10400HZ 0400Cm/s 064mmHG 0000ms
RANGE 16kHZ SWEEP 5ms DOPTEK
RANGE 16kHZ SWEEP 5ms DOPTEK
RANGE 16kHZ SWEEP 5ms DOPTEK
a
b
c

Fig 1 *Doppler echocardiographic spectral signals (range 16 kHz, sweep 5 ms) from patients with coarctation of the aorta. The transverse marker line is positioned at the maximum frequency shift which is displayed on the top left (Hz), followed by the velocity this represents (cm/s) and the gradient (mm Hg) calculated from the simple modified Bernoulli formula. The flow is mainly in systole in (a) and continues throughout diastole in (b) and (c).*

eterisation in five patients with preductal coarctation and ductus arteriosus: the pressure was higher in the main pulmonary artery than in the descending aorta in two (15 and 31 mm Hg difference), approximately equal in the two vessels in two, and 20 mm Hg lower in the main pulmonary artery in the other.

OLDER CHILDREN

Flow velocities from the ascending aorta were normal in all 25. The signal from the distal arch showed velocities of 1·4, 2·4, and 2·9 m/s in the children with recoarctation who were considered not to require further surgery and of at least 2·7 m/s (29 mm Hg) in 19 of the remaining 22. In the other three patients no high velocities away from the transducer were demonstrated. Two had previously undergone coarctation repair; one who had a patch repair when 1·2 kg in weight was shown to have a very long segment with a diameter of only 1–2 mm and the other who had end to end repair had a fibrous membrane. In the third the only demonstration of flow was a continuous signal towards the transducer (fig 2). Careful study failed to demonstrate flow through the coarctation; it proved possible to pass a French gauge 7 catheter through it but angiocardiography showed that the catheter completely occluded the lumen and that there were large collateral vessels.

INTERRUPTED AORTIC ARCH

From the suprasternal notch, with the transducer angled as if to pick up arch flow, Doppler ultrasonography showed flow away from the transducer in excess of 2·2 m/s (4·4, 3·1, and 2·3 m/s) in all three neonates with interrupted arch. Presumably this was ductal flow

COMPARISON OF PRESSURE GRADIENTS

In all 20 patients with important coarctation in whom pressures were measured on both sides, the instantaneous maximum appeared to be greater than the peak to peak gradient, the difference ranging from 1 to 6 (mean 4) mm Hg in 17 and being 9, 12, and 17 mm Hg respectively in the other three. An increased velocity jet was demonstrated in 17 of these, and comparison of the maximum Doppler gradient with the measured one gave a correlation coefficient r of 0·42 against the peak to peak ($y = 0{\cdot}46x + 26{\cdot}4$) and $r = 0{\cdot}36$ ($y = 0{\cdot}37x + 27{\cdot}2$) against the instantaneous maximum gradient. Comparison of the values by the method of Bland and Altman[6] (fig 3) confirms the poor agreement; the mean difference in gradients is −7·5 mm Hg with the differences within 2 SD being from −45·4 to 30·3 mm Hg, which is unacceptable for clinical purposes. There may have been delay in the recordings in the femoral artery but this would have given a greater instantaneous gradient, and the results suggest that in coarctation there is little difference between this and the peak to peak gradient. No relation was observed between maximum velocity (and thus gradient) and the anatomical obstruction;

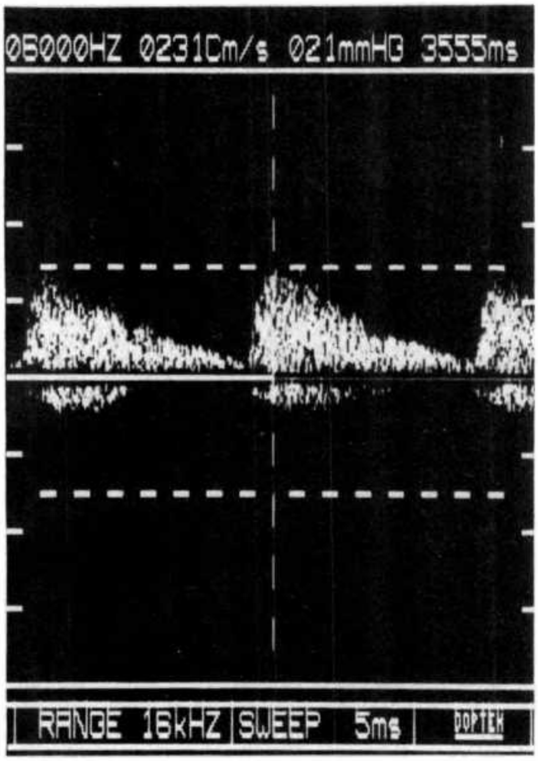

Fig 2 *Doppler echocardiographic spectral signal (range 16 kHz, sweep 5 ms) obtained from the suprasternal notch in the patient in whom the only increased velocity flow was towards the transducer, presumably through collaterals. The marker line indicates a maximum frequency shift of 6000 Hz representing a velocity of 2·31 m/s.*

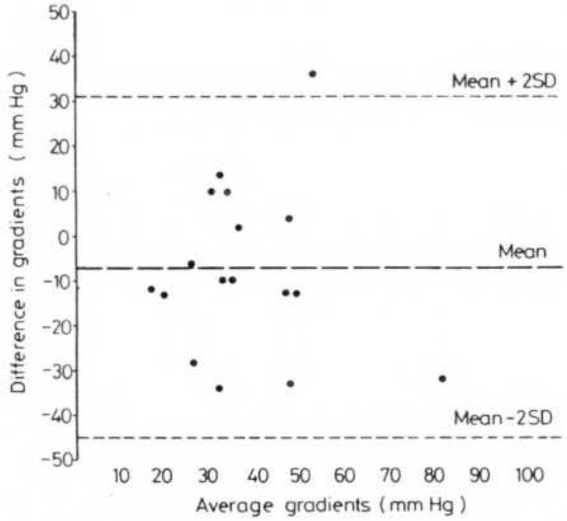

Fig 3 *Plot of tne difference between the Doppler and measured pressure gradients against their mean.*

in two patients in whom the catheter would not pass through the narrowing, Doppler estimate of gradient was 26 mm Hg in one and no flow was demonstrated in the other.

WAVE FORMS

Study of the flow patterns showed that in diastole flow was generally of low velocity and its recognition was related to the level of the high pass filter. With this set at 800 Hz (a velocity of just over 0·3 m/s) continuous flow in diastole was demonstrated in 21 of the 38 with important coarctation and increased velocity in the distal arch. In a further 10 flow apparent in early diastole did not continue throughout diastole and in seven flow was confined entirely to systole. The duration of flow was not related to the maximum velocity or gradient. The end diastolic pressure difference across the coarctation could be measured in 10 patients in whom an increased velocity was recorded; flow throughout diastole occurred in the five with a measured end diastolic gradient of ≥6 mm Hg but was not found in those with a lower gradient.

Discussion

In coarctation of the aorta Doppler ultrasound techniques might be expected to be able to confirm the presence and site of the obstruction and measure the pressure difference across it.

CONFIRMATION OF COARCTATION

Hatle and Anglesen reported that with continuous wave Doppler echocardiography a jet from beyond the coarctation could usually be obtained in patients with a moderate coarctation but in only half of those with severe obstruction[1] but Wyse *et al* found a jet in all 30 patients studied.[2] In the latter investigation, performed mainly in patients who had previously undergone coarctation repair, a good correlation was reported between the Doppler estimate of maximum velocity and the difference between blood pressures measured in the arm and leg with a sphygmomanometer, though no invasive pressure measurements were made. Robinson *et al* also published results in six infants; in three with critical aortic stenosis high velocity flow was measured in the ascending aorta whereas in three with coarctation a high velocity flow was measured in the descending aorta; this suggested that a clear distinction could be made on the basis of Doppler results.[3]

For practical purposes it is appropriate to consider the two different patient populations with coarctation, the infant with preductal coarctation and a ductus arteriosus and the others, often older patients, who usually have a postductal coarctation.

In the group with postductal coarctation our findings are more in accord with those of Hatle and Angelsen[1]; in most cases Doppler demonstrates high velocity flow but where the obstruction is very severe this may not be demonstrable. In the three children in whom Doppler did not demonstrate the high velocity there was no clinical doubt as to the presence of coarctation, however, and a site near the arch was likely in one because continuous flow towards the transducer suggested collateral flow.

Diagnosis of coarctation of the aorta in the newborn can be difficult; echocardiography is not always diagnostic and there is also the possibility of confusion between coarctation and interruption of the arch. Robinson *et al* suggested that in the neonate increased velocity flow away from the transducer indicates coarctation[3]; in one of their patients pressures on both sides of the obstruction were equal and a high velocity should not have been recorded. We speculate that the increased flow velocity in those with arch interruption is a result of ductal flow and may be wrongly interpreted as representing coarctation. It seems that ductal rather than coarctation flow may also be recorded on occasions in neonates with severe coarctation, as in the newborn infant in whom the obstruction of the ductus abolished the signal. Thus we propose that an increased velocity signal should be interpreted as indicating arch obstruction, not necessarily coarctation, because it may be found with interruption and a restrictive ductus.

MEASUREMENT OF PRESSURE DROP

Since simple measurement of arm and leg blood pressures with a sphygomomanometer will give a good estimate of the systolic pressure drop, the ability of Doppler to measure the gradient could be regarded as being of little practical clinical value. Measurement of leg blood pressure, however, can be difficult and in some patients who have undergone coarctation repair the use of arteries for the repair, pressure monitoring, or cardiac catheterisation can occasionally make measurement of arm blood pressure unreliable.

Although we have found a good correlation between catheter and Doppler derived gradients for other obstructive lesions,[7-9] the present study has shown that in our laboratory the simple Bernoulli formula does not give a good correlation with direct pressure as we recorded it. Nor can the poor agreement be attributed to the difference between instantaneous maximum and peak to peak gradients, which in our experience is negligible.

Doppler echocardiography might have been expected to underestimate the pressure gradient in some patients with coarctation either because of misalignment with the direction of flow or because it is known to give low values where the orifice is small,[10] especially if the narrowed segment is long.[11] It is less easy, however, to explain the overestimation of gradient by more than 20 mm Hg in three children; the study was performed at catheterisation in all three and in only one was the distal pressure measured while a catheter was through the coarctation. It may be that this was collateral flow but the direction and velocity were different from that in the one child where this was considered to have been clearly demonstrated (fig 2).

Since the measurement of pressure gradient with continuous wave Doppler has proved reliable in other situations with discrete obstruction it is difficult to explain why it should overestimate the gradient in some patients with coarctation. This may be due in part to the use of the modified Bernoulli formula, $\Delta P = 4V^2$, which does not take the proximal velocity into account, thus potentially overestimating the pressure drop. The discrepancy may also be related to the measurement technique, in all three the distal pressure having been recorded from the femoral artery. At catheterisation the pressure in the femoral artery can be higher than in the ascending aorta[12] because of the progressive distortion of the pressure wave as it is transmitted through the arterial system.[13] It is not certain whether this applies in coarctation, but the measured gradient may have underestimated the true one and Doppler estimation may well be more accurate than the results presented in this study suggest.

This study has shown that although in most patients Doppler echocardiography allows an accurate demonstration and localisation of coarctation of the aorta, the findings should be interpreted with full knowledge of the weaknesses of the technique and within the context of the whole clinical and noninvasive investigation. The results suggest that in the newborn infant extreme caution must be exercised; the presence of an increased velocity is likely to indicate coarctation but can also be found with a restrictive ductus arteriosus with interruption (or very severe coarctation). Since good images of the aortic arch are usually obtained from these babies it may be that Doppler echocardiography has little to add to clinical examination and conventional cross sectional echocardiography in this situation. In older children it can be difficult to demonstrate the coarctation by cross sectional echocardiography and Doppler echocardiography will often indicate its presence and site. In very severe obstruction, however, the failure of Doppler echocardiography to show an increased velocity in the presence of clinical coarctation requires reassessment of the noninvasive information and might even indicate the need for angiography. When a signal suggesting the presence of coarctation is obtained the maximum velocity (and thus Doppler gradient) does not correlate with the anatomical severity of the narrowing. Furthermore, our findings indicate that Doppler echocardiography may be less accurate in measuring pressure gradients in coarctation than in other obstructive lesions and we believe that further correlative studies are needed.

References

1 Hatle L, Angelsen B. *Doppler ultrasound in cardiology: physical principles and clinical applications.* Philadelphia: Lea and Febiger, 1985:217–20.

2 Wyse RKH, Robinson PJ, Deanfield JE, Tunstall Pedoe DS. Use of continuous wave Doppler ultrasound velocimetry to assess the severity of coarctation of the aorta by measurement of aortic flow velocities. *Br Heart J* 1984;52:278–83.

3 Robinson PJ, Wyse RKH, Deanfield JE, Franklin R, Macartney FJ Continuous wave Doppler velocimetry as an adjunct to cross sectional echocardiography in the dignosis of critical left heart obstruction in neonates. *Br Heart J* 1984;52 552–6.

4 Hatle L, Brubakk A, Tromsdal A, Angelsen B. Noninvasive assessment of pressure drop in mitral stenosis of Doppler ultrasound. *Br Heart J* 1978;40:131–40.

5 Wilson N, Goldberg SJ, Dickinson DF, Scott O. Normal intracardiac and great artery blood velocity measurements by pulsed Doppler echocardiography. *Br Heart J* 1985;53:451–8.

6 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307–10.

7 Houston AB, Sheldon CS, Simpson IA, Doig WB, Coleman EN. The severity of pulmonary valve or artery obstruction in children estimated by Doppler ultrasound. *Eur Heart J* 1985;6:786–90.

8 Simpson IA, Houston AB, Sheldon CD, Hutton I, Lawrie TDV. Clinical value of Doppler echocardiography in the assessment of adults with aortic stenosis. *Br Heart J* 1985;53.636–9

9 Houston AB, Simpson IA, Sheldon CD, Doig WB, Coleman EN Doppler ultrasound in the estimation of the severity of pulmonary infundibular stenosis in infants and children. *Br Heart J* 1986;55·381–4.

10 Holen J, Aaslid R, Landmark K, Simonsen S, Ostrem T. Determination of effective orifice area in mitral stenosis from non-invasive ultrasound Doppler data and mitral flow rate. *Acta Med Scand* 1977;**201**:83–8

11 Teirstein PS, Yock PG, Popp RL The accuracy of Doppler ultrasound measurement of pressure gradient across irregular, dual and tunellike obstructions to blood flow. *Circulation* 1985;72:577–84.

12 Verel D, Granger RG. *Cardiac catheterization and angiocardiography.* Edinburgh, London, New York· Churchill Livingstone, 1978:13.

13 Remington JW, O'Brien LJ. Construction of aortic flow pulse from pressure pulse. *Am J Physiol* 1970,**218**.437–47.

Br Heart J 1987;57:44–50

A new non-invasive estimation of the stenotic aortic valve area by pulsed Doppler mapping

COLETTE VEYRAT,* C GOURTCHIGLOUIAN, P DUMORA, G ABITBOL, D SAINTE BEUVE, D KALMANSON

From the Service de Cardiologie, Fondation A de Rothschild, Paris, France

SUMMARY A new pulsed Doppler mapping technique has been used to measure the severity of aortic valve stenosis. The Doppler examination was performed at the site of the aortic orifice in the parasternal short axis echocardiographic view and the method was based on the detection of the area of systolic flow through the stenotic orifice. This area was derived by planimetry and the measurements obtained by the Doppler method were compared with the aortic valve area calculated at catheterisation according to the Gorlin formula. The method was applicable in 41 of the 44 patients studied. The Doppler data were consistent with the haemodynamic measurements even in patients with decreased cardiac index.

It is concluded that this new application of the flow mapping procedure is reliable and is easily applied to adult patients with a wide range of clinical conditions.

Knowledge of the aortic valve area is important in the management of patients with aortic stenosis. In adults standard non-invasive procedures have failed to provide a variable that reliably predicts the aortic valve area.[1-3] Doppler echocardiography would be expected to be the most appropriate of recent developments because it measures flow. Aortic stenosis can be measured by continuous wave Doppler. This method relies on the calculation of the pressure gradient across the orifice.[4-6] The shortcoming of this variable is that it is dependent on cardiac output. The semilunar stenotic area has been calculated by non-invasive measurement of both the pressure gradient and cardiac output in children.[7] Non-invasive measurement of the cardiac output is feasible in adults,[8 9] but is not yet routinely applicable particularly in elderly patients and in a recent attempt to calculate the aortic valve area with continuous wave Doppler in an adult population invasive measurement of cardiac output was still required.[10] We present a new non-invasive method of measuring aortic stenosis with pulsed Doppler. It is based on flow mapping at the aortic orifice, which is used to delineate the aortic valve area. To assess the reliability of the new procedure we have compared it with results derived from catheterisation.

Patients and methods

We studied 44 consecutive patients (21 men and 23 women (mean age 58)) with aortic stenosis who underwent left heart catheterisation. Forty two patients were in sinus rhythm and two were in atrial fibrillation. The aetiology was congenital (2), rheumatic (12), or degenerative with calcified aortic cusps (30). The stenosis was sometimes associated with regurgitation; this was graded as minimal in seven cases and as moderate in five other cases. The other associated abnormalities were mitral stenosis (6), or prosthesis (2), tricuspid regurgitation (7), cardiomyopathy (2), coronary heart disease (4), and angiodysplasia (1). Twenty eight patients later had surgery.

We also studied a control group of 12 patients (7 men and 5 women (mean age 47 years)) with no aortic gradient at cardiac catheterisation. All but one were in sinus rhythm. Diagnoses were mitral stenosis (6), non-obstructive cardiomyopathy (3), coronary heart disease (2), and atrial septal defect. (1).

INVASIVE PROCEDURES

The diagnosis was assessed by means of left heart

Requests for reprints to Dr Colette Veyrat, Service de Cardiologie, Fondation A de Rothschild, 25–29 rue Manin, 75940 Paris Cedex 19, France.

*Chargé de Recherches au CNRS.

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retrograde or transseptal catheterisation, or both, by standard techniques. The aortic valve area was calculated according to the Gorlin formula.[11] Cardiac output was measured by the Fick method or thermodilution, or both. Supravalvar aortography was performed from a 30° or 45° right anterior oblique position. The severity of the regurgitation was assessed by qualitative criteria on a three point grading scale.[12]

DOPPLER ECHOCARDIOGRAPHY

We used a 3 MHz ATL 851 (Squibb Medical System, Bellevue, Washington, USA) mechanical real time scanner, which provided a 90° sector and single gate steerable pulsed Doppler capability, with a tear drop shaped (2 × 4 mm) sample volume.[13] The Doppler output could be presented as an audible signal, a time interval histogram, and a real time frequency spectrum by means of fast Fourier transform analysers. These devices were either an Angioscan (Unigon Industries, Mount Vernon, NY, USA), or a Sonacolor (Carolina Medical Electronics, King, NC, USA). The principles and characteristics of the instruments have been described elsewhere.[14 15]

We used two video monitors, one for real time scanning and the other for the Doppler display. Hard copies of real time images were made on a 4633 Tektronics recorder. M mode echocardiographic tracings, simultaneous electrocardiograms, phonocardiograms, and Doppler spectral displays were recorded on an Irex 101 (Irex, Mahwah, NJ, USA) multitrace recorder or on Polaroid films.

Subjects were generally studied in the left lateral supine position within a few days of catheterisation. The method of cross sectional Doppler echocardiographic examination of the heart[16] that we used requires dynamic visualisation of the structure or chamber under investigation, location of the Doppler beam seen as a white line crossing the area of interest, and adjustment of the Doppler gate, seen as a white spot, to control the depth of the sample volume along that beam. The image is then frozen while the apparatus is automatically switched to the Doppler system. When the characteristic Doppler sound is heard, the recording is performed.

EXAMINATION OF THE AORTIC VALVE ORIFICE (FIG 1A)

We used the left parasternal short axis view to get a satisfactory image of the aortic orifice. Visualisation of part of the tips of the cusps indicated that the Doppler beam was located in the plane required. In

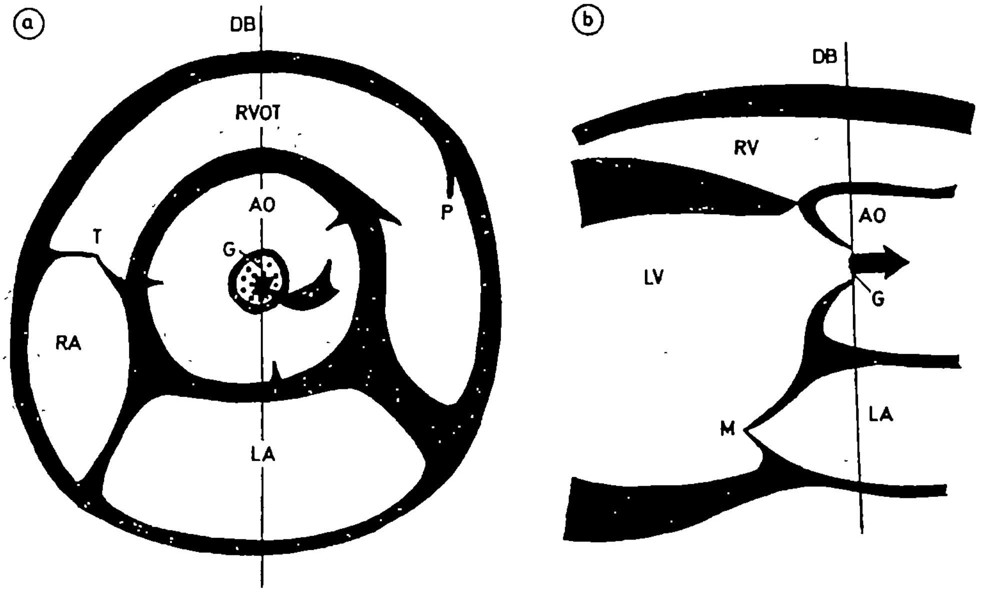

Fig 1 *Schematic representation of the mapping procedure used for measuring the stenotic aortic valve area in aortic stenosis. (a) Mapping of the stenotic aortic valve area (dotted area) in short axis echocardiographic view. The Doppler beam (vertical line) transects the aortic orifice and the Doppler gate is moved over the orifice to detect a systolic flow signal (arrow). The limits of the area are defined by to-and-fro scanning movements from the centre to the boundary edges. (b) Determination of the tips of the cusps by long axis examination. The Doppler beam is located beyond the cusps (vertical line), and the Doppler gate detects the area of systolic flow (arrow) along the anteroposterior axis of the aortic root. (AO, aortic orifice; DB, Doppler beam; G, Doppler gate; LA, left atrium; LV, left ventricle; M, mitral valve; P, pulmonary valve; RA, right atrium; RV, right ventricle; RVOT, right ventricle outflow tract; T, tricuspid valve*

patients with important calcification the transducer was oriented slightly upwards. Once the cusps had been visualised the image was frozen in systole and the following procedure was performed. We carefully searched for a Doppler signal with maximum amplitude and duration occurring before the end of systole whether it was positive, negative, or both. When this signal was detected we performed to-and-fro mapping of the area where it was recorded, from its centre to its boundary edges, along its anteroposterior, transverse, and oblique axes to obtain a measure of the aortic valve area. A sheet of transparent plastic was applied over the video monitor and the contour of the area was traced either during subsequent repeated manoeuvres or during a later review of the video tape. We took care to avoid parallax errors. We also mapped the entire aortic orifice using the same procedure to define the anatomical relations of the stenotic area to the orifice.

During the examination we paid particular attention to the following points. To minimise artefact due to motion of the aortic area during systole, the timing of early systole was noted when we determined the first location point of the mapping and this was maintained for the determination of all subsequent mapping points; to check that the site of the recording coincided exactly with the plane of the aortic orifice we crosschecked the anteroposterior measurement (in millimetres) obtained in the short axis view against that obtained in long axis view at the tip of the aortic cusps using the same Doppler criteria (fig 1b). If necessary, in the case of eccentric areas leading to eccentric flow signals, we used a manoeuvre derived from that proposed by Nishimura *et al* for the mitral apparatus,[17] that is we used two complementary parallel long axis views transsecting the long axis of the heart on each side of the central long axis view.

Three sequences of systolic beats were analysed and averaged to determine the measurements. All patients were examined without knowledge of the results of the invasive procedures, which were performed by separate teams. The first 31 patients were investigated by two independent observers. Each videotape was reviewed by each observer within three weeks of the examination and there was no significance intraobserver discrepancy between the results.

The stenotic valve areas were measured by planimetry with a Hewlett Packard integrator 98134 A with a 1% error estimated from planimetry of test areas of given values. For the statistical study, each pair of values was displayed together with the line of equality, both for the aortic valve area and for the study of interobserver agreement. The variance of the paired measurements was also studied and the differences between the measurements obtained from both methods were plotted against the mean value of these measurements to study the agreement between the methods.[18]

Results

CONTROLS

An audiosignal of flow with smooth tone was heard over most of the aortic orifice in all patients. The graphic display showed a net velocity vector away from the zero line in only five patients. Among the remaining patients the signal was too weak to generate such a deflection, and the graphic display consisted of an early and mid-systolic broadened spectrum between two transient velocity deflections due to cusp motion that was widely spread over the orifice, with a harsher tone when approaching the boundary edges (fig 2).

PATIENTS WITH AORTIC STENOSIS (TABLE 1, FIGS 3–6)

Recordings were unsatisfactory in three patients because of poor signal to noise ratio. The Doppler

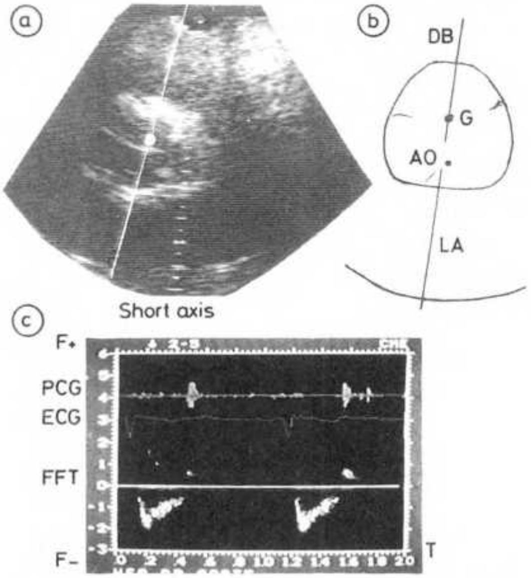

Fig 2 *Normal aortic orifice. (a) Short axis scan view of the aortic orifice with the Doppler gate shown in the centre of the orifice on the schematic drawing (b). (c) Pulsed Doppler recording of systolic flow obtained by fast Fourier transform spectral analysis. There is a systolic deflection away from the zero line with a laminar spectrum. This signal was heard over most of the aortic area in this patient. In half the patients with normal aortic valves no clear deflection was seen. Instead there was an early systolic spectral broadening recorded over most of the aortic orifice. See legend to fig 1 for abbreviations. FFT, fast Fourier transform; ECG, electrocardiogram; PCG, phonocardiogram; F+ and F−, positive and negative Doppler shifts; T, time axis.*

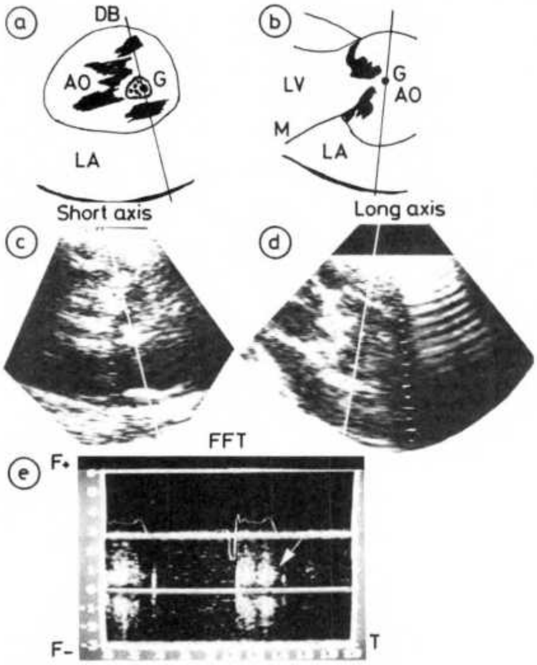

Fig 3 *Patient with aortic stenosis. Drawings of the short axis (a) and the long axis (b) views of the aortic orifice. The gate is located at the site of the narrowing area (stippled area). Scan views of both planes in which the aortic orifice was visualised (c and d). (e) Real time Doppler recording of spectral analysis showing the systolic spectral anomalies (white arrow) peaking before end systole. No Doppler flow signal was recorded over the remaining orifice area. See figures 1 and 2 for abbreviations.*

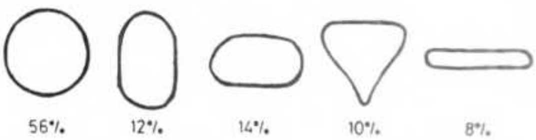

Fig 4 *Various shapes of stenotic areas found by the flow mapping procedure. The frequency (%) of each type of stenotic area is indicated. Only three patients (8%) had a slit shaped orifice. Two of them were operated upon and were found to have a Monckeberg disease.*

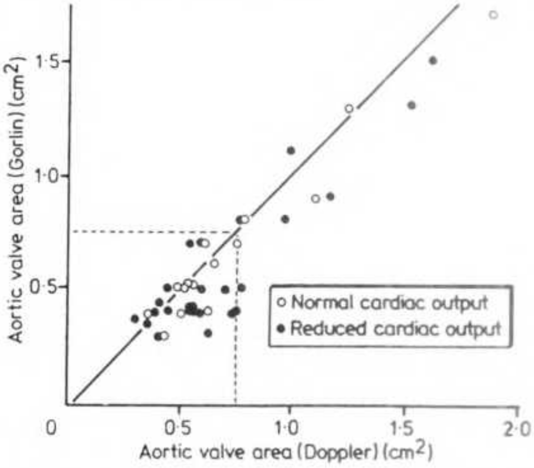

Fig 5 *Plot of Doppler and invasive measurements of the aortic valve area showing line of equality. A cardiac index of < 3 l/min/m² was regarded as indicating a decreased cardiac output. The linear correlation coefficient was 0·94. It was 0·91 when cardiac output was reduced and 0·96 when it was normal. The area within the dotted lines corresponds to critical areas ≤ 0·75 cm².*

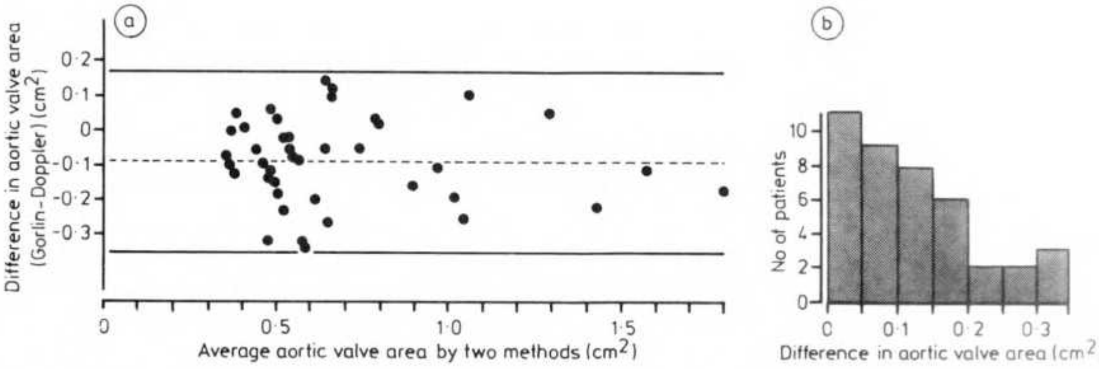

Fig 6 *Differences between non-invasive and invasive measurements of the aortic valve area. (a) Differences plotted against mean value for both measurements (horizontal axis). Dotted line represents the mean value of the differences. The limits of agreement are shown. The standard error of the mean was 0·02 cm². (b) Absolute values of the differences between both measurements are shown on the abscissa and the number of patients with a particular value is shown on the ordinate.*

findings were characterised by the absence of an audiosignal of systolic flow over the aortic orifice, except for a restricted area where there was a harsh tone. The corresponding graphic display showed a broadened spectrum over the first two thirds of systole, with a mid-systolic window in some cases. Velocity signals due to cusp motion could also be heard. The narrowed area was generally round (23) or ovoid with a major anteroposterior (5) or transverse (6) axis. More rarely it was triangular (4) or a transverse slit (3). It was located at the centre of the orifice in 18 patients and eccentrically in 23 patients. Doppler prediction of the site of the narrowed orifice was confirmed in nine patients at operation (six central and three eccentric locations). Two patients showing a slit like central area at Doppler examination were found to have a Monckeberg sclerosis without commissural fusion. In the remaining patients who came to operation correlation between the Doppler findings and direct examination was made impossible by conspicuous calcifications. Table 1 shows individual and mean values of haemodynamic and Doppler data. Only one patient (case 25) was erroneously classified as having an aortic valve flow area $>0{\cdot}75\,cm^2$ at Doppler. The mean value of the aortic valve area was larger (NS) at Doppler than at catheterisation. Figure 5 shows the values of the measurements with the line of equality. The mean difference was $-0{\cdot}09\,cm^2$ with a standard deviation of 0·13. The limits of agreement ranged from −0·35 to $+0{\cdot}17\,cm^2$ (fig 6a). Figure 6b shows that in 20 patients the difference did not exceed $0{\cdot}10\,cm^2$. The greatest differences were 0·33, 0·32, $0{\cdot}35\,cm^2$ and these were found in patients with values of 0·4 (case 16), 0·3 (case 21), and $0{\cdot}4\,cm^2$ (case 31) respectively by the Gorlin formula.

Figure 7 shows two observers' measurements with

Table *Invasive determination of cardiac index and stenotic aortic valve areas by the Gorlin formula and the pulsed Doppler mapping procedure in patients with aortic stenosis*

			Stenotic aortic valve area (cm^2)	
Case No	*Age (yr)*	*Cardiac index (l/min/m^2)*	*Gorlin formula*	*Pulsed Doppler*
1	61	2·1	0·8	0·77
2	79	2·6	0·4	0·55
3	71	3·1	0·5	0·52
4	71	2·7	0·35	0·35
5	73	3·2	0·6	0·65
6	79	3·1	0·5	0·59
7	36	2·8	0·4	0·59
8	78	3·1	0·4	0·63
9	73	2·4	0·8	0·96
10	69	1·9	0·3	0·38
11	10	3·1	0·4	0·35
12	31	3·4	0·5	0·47
13	53	3·4	1·7	1·87
14	72	2·7	0·4	0·39
15	56	2·1	0·3	0·4
16	76	2·2	0·4	0·73
17	60	2·4	0·5	0·59
18	49	2·6	1·5	1·61
19	37	1·7	0·4	0·54
20	16	3·1	0·7	0·75
21	80	1·7	0·3	0·62
22	38	3·06	0·5	0·56
23	19	3·2	0·5	0·52
24	64	2·05	0·5	0·44
25	66	2·8	0·5	0·77
26	57	3·0	0·4	0·5
27	82	2·7	0·4	0·45
28	68	3·3	0·3	0·43
29	77	2·0	0·4	0·54
30	34	3·0	0·8	0·76
31	71	2·5	0·4	0·75
32	73	2·1	0·5	0·70
33	69	3·2	0·9	1·1
34	69	2·6	0·7	0·54
35	64	2·0	0·7	0·59
36	65	2·6	0·9	1·17
37	24	2·3	1·3	1·52
38	73	3·1	1·3	1·24
39	68	2·5	1·1	0·99
40	62	2·4	0·9	1·00
41	34	3·0	0·7	0·58
Mean value (SD)	58 (19)	2·65 (0·48)	0·63 (0·34)	0·72 (0·35)

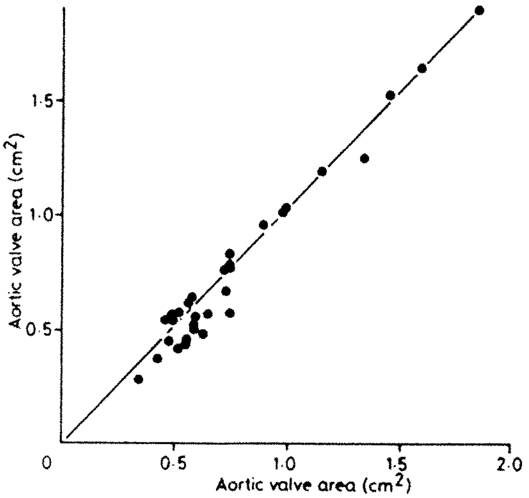

Fig 7 *Measurements of the aortic valve area performed by two independent observers. There was good agreement between the measurements performed on 31 patients by two observers. The line of equality is shown. (SEM 0·01 cm^2, correlation coefficient 0·95).*

the line of equality. The mean difference was 0·02 cm^2 with a standard deviation of 0·08.

Discussion

In the present study we used mapping of the aortic valve area to quantify previously diagnosed aortic stenosis. The rationale of our method, which is based on measurements derived from the flow mapping procedure, has already been described and discussed for tricuspid[19] and left sided regurgitation.[20]

Our results show that the Doppler mapping procedure provided a satisfactory assessment of the areas of flow. There was only one minor error of classification. Despite the good correlation between the invasive and the non-invasive data (fig 5), agreement between both methods was not complete; Doppler measurements often exceeded the values found at catheterisation. Figure 6b shows that the differences were, however, often minimal, but with some instances of larger variation. Is this variability in the measurements clinically acceptable? When the severity of aortic stenosis is assessed the aim is to detect or exclude the need for operation—that is a flow area of $\leq$0·75 cm^2. Figure 5 shows that the variability of the measurements did not affect the assessment of patients with large stenotic areas (close to or above 1 cm^2). Nor did it affect the efficiency of the new method in detecting all but one of the critical areas despite very wide differences between the invasive and non-invasive measurements in three patients. In these three patients the invasive values were considerably less than 0·75 cm^2, which is often the case in severe stenosis. The range of areas $<$0·75 cm^2 and $>$1 cm^2 covers most clinical situations. When the size of a stenotic orifice lies close to the critical value of 0·75 cm^2, however, the variability in measurements might lead to misclassification. In our study there was only one error of this type.

One explanation of the variability of the measurements may be insufficient spatial resolution of the sample volume. Spatial resolution varies with the depth of the recording site and with the size and shape of the sample volume. The width of the latter is determined by the beam width and the length by the pulse envelope. If the attenuation of the ultrasound intensity is limited by a factor of 2 (6 DB) the sample volume will be an ellipsoid with a length of 1·5 mm (three sine waves of 3 MHz) and width of 1·5–2 mm (or stated more simply, a sphere of 2 mm diameter).[21] The accuracy of the mapping procedure depends on the accuracy of the determination of the absence of flow at the edges of the area. This will be least accurate at positions between 2 and 3 (fig 8); theoretically this error will be very small because of the decreased energy of the 3 MHz ultrasound wave reflected from both these positions. In most cases these errors are likely to be reduced by other factors, mainly the high pass filters of the velocimeter and the well known sharp decrease of the jet velocity profile within 0·5 mm to 1 mm of the edges. In some cases, however, the determination of the limits of flow might be affected by the extension of the boundary layer over a wider cross section of the jet than usual, as was shown experimentally in tight stenoses.[22] This could lead to inaccuracy and might explain the scattered values for critical areas within the 0·75 cm^2 limits on fig 5.

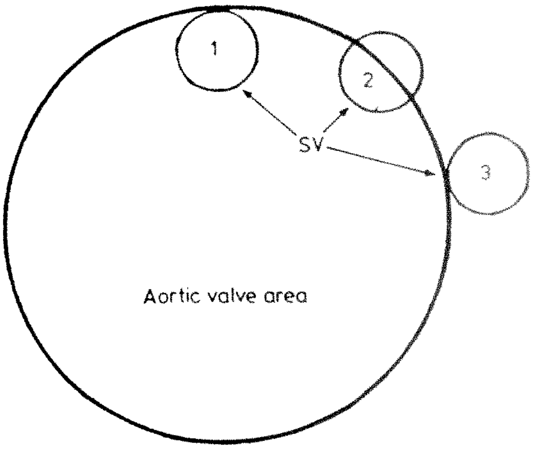

Fig 8 *Schematic representation of the different positions of the sample volume along the border of the flow area. See text for explanation. SV, sample volume.*

Two other causes of variability between Doppler and invasive measurements should also be kept in mind. Firstly, the plane of the Doppler examination may differ slightly from that at which the jet starts. This is most unlikely to have occurred in our study because of the high correlation found between the measurements of the anteroposterior axis of the flow area obtained from short and long axis views. The long axis view ensured that the measurement was performed at the tips of the aortic valves. Secondly, the Gorlin formula produces an average figure by unit of time, representing a functional value of the area, whereas the Doppler measurements correspond to the area of instantaneous flow passing through an anatomical orifice. In addition, the Gorlin formula takes into account the contraction coefficient of the jet after its starting point; this may account for some of the observed differences between both values. Surgical or pathological correlation was available in only a few cases. The relatively high percentage (44%) of asymmetrical orifices shows that caution is required in using a single diameter to calculate the true area.

As with all ultrasonic procedures a poor signal to noise ratio may limit the clinical application but future technological improvements should improve performance. Although the newer flow mapping multigate devices should make the procedure easier, they will also be affected by the problem of spatial resolution. The presence of low cardiac output is not a limiting factor because the new procedure remained accurate throughout the clinical range.

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References

1 Benchimol A, Dimond EG, Shen Y. Ejection time in aortic stenosis and mitral stenosis. *Am J Cardiol* 1980;5:728–39.

2 Weyman AE, Feigenbaum H, Dillon JC, Chang S. Cross sectional echocardiography is assessing the severity of valvular aortic stenosis. *Circulation* 1975;52:828–34.

3 DeMaria AN, Bommer W, Hoye J, Lee G, Bouteller J, Mason DT. Value and limitations of cross sectional echocardiography of the aortic valve in the diagnosis and quantification of valvular aortic stenosis. *Circulation* 1980;**62**:304–12.

4 Hatle L, Angelsen BA, Tromsdal A. Non-invasive assessment of aortic stenosis by Doppler ultrasound. *Br Heart J* 1980;**43**:284–92.

5 Stamm RP, Martin RP. Quantification of pressure gradients across stenotic valves by Doppler ultrasound. *J Am Coll Cardiol* 1983;**2**:707–18.

6 Hoffmann A, Burckhardt D. Evaluation of systolic murmurs by Doppler ultrasonography. *Br Heart J* 1983;**50**:337–42.

7 Kosturakis D, Allen HD, Goldberg SJ, Sahn DJ, Valdes Cruz LM. Non invasive quantification of stenotic semilunar valve areas by Doppler echocardiography. *J Am Coll Cardiol* 1984;**3**:1256–62.

8 Griffith J, Henry WL. An ultrasound system for cardiac imaging and Doppler blood flow measurement in man. *Circulation* 1978;**56**:925–30.

9 Goldberg SJ, Sahn DJ, Allen HD, Valdes Cruz LM, Hoenecke H, Carnahan Y. Evaluation of pulmonary and systemic blood flow by two-dimensional Doppler echocardiography using fast Fourier transform spectral analysis. *Am J Cardiol* 1982;**50**:1394–400.

10 Warth DC, Stewart WJ, Block PC, Weyman AE. A new method to calculate aortic valve area without left heart catheterisation. *Circulation* 1984;**70**:978–83.

11 Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves and central circulatory shunts. *Am Heart J* 1951;**41**:1–29.

12 Carrillo Kabana J, Calderon Montero J, Lopez Sendon J, Fuertes Garcia A, Pey-Illera J. Qualitative and quantitative evaluation of aortic and mitral insufficiencies. Comparative study. *Rev Esp Cardiol* 1976;**29**:227–35.

13 Johnson SL, Baker DW, Lute R, Dodge HT. Doppler echocardiography. The localization of cardiac murmurs. *Circulation* 1973;**48**:810–27.

14 MacPherson PC, Meldrum SJ, Tundstall Pedoe DS. Angioscan: a spectrum analyser for use with ultrasonic Doppler velocimeters. *J Med Eng Technol* 1981;5:84–5.

15 Spencer MP, Fujioka K. CW Doppler with spectral analysis in acquired valve disease. In: Spencer MD, ed. *Cardiac Doppler diagnosis*. Boston: Martinus Nijhoff, 1983:153–74.

16 Veyrat C, Kalmanson D, Farjon M, Guichard JP, Sainte Beuve D, Abitbol G. Combined pulsed Doppler echocardiography for the investigation of valvular heart diseases: one dimensional versus two dimensional approach. In: Rijsterborgh H, ed. *Echocardiology*. Boston: Martinus Nijhoff, 1981:291–8.

17 Nishimura K, Sakakibara T, Hibi N, *et al.* High speed ultrasonocardiotomography: echocardiographic manifestations of papillary muscles and chordae tendineae. *J Cardiogr* 1977;7:1–13.

18 Bland JM, Altman DG. Statistical method for assessing agreement between two methods of clinical measurement. *Lancet* 1986;i:307–10.

19 Miyatake K, Okamoto M, Kinoshita N, *et al.* Evaluation of tricuspid regurgitation by pulsed Doppler and two dimensional echocardiography. *Circulation* 1982;**66**:777–84.

20 Veyrat C, Abitbol G, Bas S, Manin JP, Kalmanson D. Quantitative assessment of valvular regurgitation using the pulsed Doppler technique. Approach to the regurgitant lesion. *Ultrasound Med Biol* 1984;**10**:201–13.

21 Jorgensen JE, Campau DN, Baker DW. Physical characteristics and mathematical modelling of the pulsed ultrasonic flowmeter. *Med Biol Eng* 1973;**11**:404–21.

22 Holen J. Quantification of flow obstruction in mitral stenosis and prosthetic mitral valves with Doppler ultrasound. In: Spencer MP, ed. *Cardiac Doppler diagnosis*. Boston: Martinus Nijhoff, 1983:337–42.

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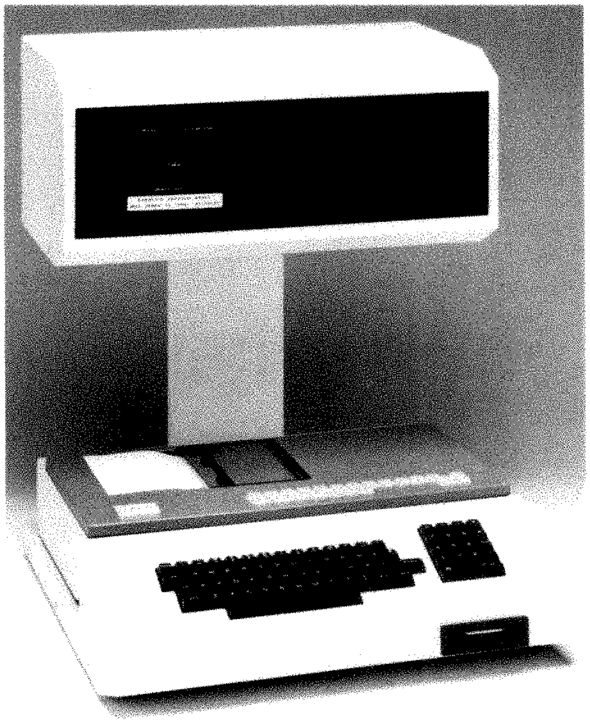

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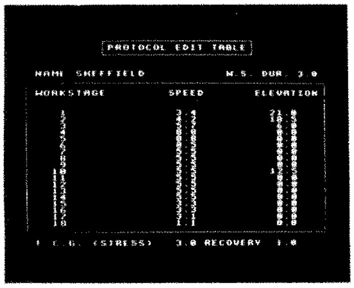

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PROTOCOL EDIT TABLE

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E.C.G. (STRESS)   3.0 RECOVERY  1.0
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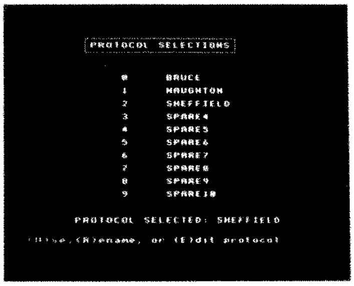

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PROTOCOL SELECTIONS

    0       BRUCE
    1       NAUGHTON
    2       SHEFFIELD
    3       SPARE4
    4       SPARE5
    5       SPARE6
    6       SPARE7
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    8       SPARE9
    9       SPARE10

PROTOCOL SELECTED: SHEFFIELD
(U)se,(R)ename, or (E)dit protocol
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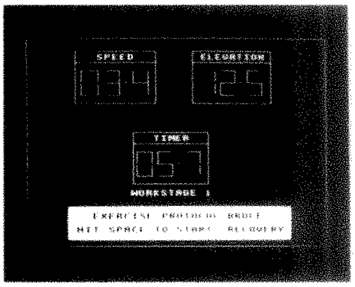

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SPEED        ELEVATION
13.4         12.5

    TIMER
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WORKSTAGE 1

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Br Heart J 1987;57:51–3

Case reports

Percutaneous balloon valvotomy in tricuspid stenosis

MUAYED AL ZAIBAG, PAULO RIBEIRO, SAAD AL KASAB

From the Adult Cardiology Division, Riyadh Cardiac Centre, Kingdom of Saudi Arabia

SUMMARY This report describes the first successful treatment of tricuspid stenosis by percutaneous double balloon valvotomy. There was a dramatic reduction of the tricuspid valve gradient, with an increase in calculated valve area, together with an increase in resting cardiac output and symptomatic relief. The feasibility of the non-surgical treatment of severe tricuspid stenosis was demonstrated unequivocally.

Non-surgical balloon valvotomy has become an established treatment for pulmonary stenosis,[1] and the technique is currently being assessed for the treatment of aortic and mitral stenosis.[2 3] A single balloon was used in these studies; however, we have recently reported the advantages of a double balloon technique for mitral valvotomy.[4]

We report the first successful treatment of tricuspid stenosis by percutaneous double balloon valvotomy. This case was selected for this treatment because of the unusual combination of severe rheumatic tricuspid stenosis, with only trivial incompetence, and mild mitral stenosis.

Case report

A 45 year old labourer with a history of rheumatic fever presented with fatigue that limited his capacity to work and mild exertional dyspnoea. Examination showed sinus rhythm and a prominent "a" wave in the jugular venous pulse. Blood pressure was 130/85 mm Hg. The cardiac impulse was normal. A diastolic thrill and murmur at the lower left sternal edge radiated to the apex; there was presystolic and inspiratory accentuation. The electrocardiogram showed biatrial enlargement with a right atrial vector of 0·4 mV and no evidence of right ventricular hypertrophy. The chest *x* ray was unremarkable.

Rheumatic tricuspid stenosis was confirmed by cross sectional echocardiography which showed thickening and doming of all three leaflets. Before cardiac catheterisation the patient was treated with digoxin and propranolol. Cardiac output was calculated by the thermodilution technique. The mitral and tricuspid gradients were calculated by planimetry and valve areas by the Gorlin formula. Angiographically there was a thickened and domed tricuspid valve with trivial incompetence. The haemodynamic findings indicated severe tricuspid stenosis (fig 1 and table). There was mild mitral stenosis; the valve area was 2·0 cm.^{2}

Technique of tricuspid double balloon valvotomy

Informed consent was obtained. Ten mg of diazepam was given orally as premedication and propranolol was continued. An 18 gauge cannula was inserted into the right femoral artery for pressure monitoring. A 7 French Berman angiocatheter was passed from each femoral vein to measure the pressure gradient across the tricuspid valve and to perform a right ventricular angiogram before and after balloon inflation. After calibration and the recording of identical simultaneous right atrial pressure tracings from both catheters, one catheter was advanced to the right ventricular cavity. Ten consecutive cardiac cycles were recorded at a paper speed of 100 mm/s to measure the gradient across the tricuspid valve. The mean tricuspid gradient was only accepted after two identical simultaneous right atrial pressure traces had been recorded after the withdrawal of the right ventricular catheter back into the right atrium.

The 0·038 inch Teflon coated exchange guide wires (250 cm long) with curved tips were advanced through two 7 French pigtail catheters, which previously had been inserted percutaneously in each femoral vein. The curved end of each wire was positioned at the apex of the right ventricle (fig 2). A 9 French balloon catheter (Meditech; 15 mm diameter, 3 cm length) was advanced percutaneously

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Requests for reprints to Dr Muayed Al Zaibag, Adult Cardiology Division, Riyadh Cardiac Centre, Riyadh Military Hospital, PO Box 7897, Riyadh 11159, Kingdom of Saudi Arabia.

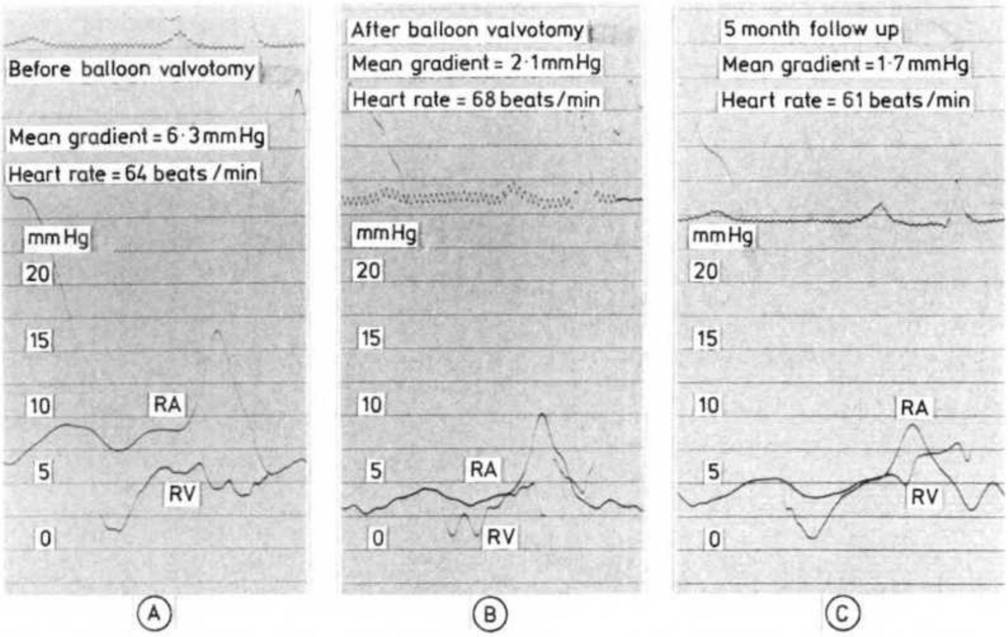

Fig 1 *Right atrial (RA)/right ventricular (RV) pressure gradient recording before (A), immediately after (B), and five months after (C) successful balloon tricuspid valvotomy. Note the reduction in the gradient and "a" wave amplitude.*

over each guide wire and positioned across the tricuspid valve under fluoroscopic control in the 10° right anterior oblique projection. The balloons were correctly positioned across the tricuspid valve with the aid of injections of contrast media into the right atrium, and the positioning was confirmed by fluoroscopic detection of the indentation of the balloon during inflation. The balloons were inflated simultaneously on three occasions to a maximum pressure of 5 atmospheres (505 kN/m^2). There was no reduction in the tricuspid gradient and no balloon indentation occurred during these inflations. Therefore, we replaced one of the 15 mm diameter balloon catheters with a 20 mm diameter balloon that was slid over the exchange guide wire which was left in position. The balloons were inflated three more times. During the third inflation proper balloon alignment was achieved, with indentation of one balloon (fig 2). Disappearance of this indentation, together with the subsequent considerable reduction in the gradient, was taken to indicate a successful result.

Table *Haemodynamic findings before balloon tricuspid valvotomy (A), immediately after (B), and at 5 month follow up (C)*

Variable	*A*	*B*	*C*
Heart rate/min	64	68	61
Cardiac index ($l/min/m^2$)	2·1	2·3	2·8
Pre "a" wave gradient (mm Hg)	3·0	0·0	0·0
Mean gradient (mm Hg)	6·3	2·1	1·7
Valve area (Gorlin) (cm^2)	0·9	2·0	2·3

All inflations lasted for 8–12 s, and during this time the systolic systemic arterial pressure remained > 80 mm Hg.

Results

There was a considerable improvement in haemodynamic variables immediately after balloon tricuspid valvotomy (table). At five month follow up, while the patient was still taking propranolol to maintain a similar heart rate, the haemodynamic improvement persisted. Biplanar right ventriculography showed no increase in tricuspid regurgitation. The patient reported virtually normal effort tolerance and he had returned to his previous job. At clinical examination we found that the thrill and the long diastolic rumble had disappeared.

Discussion

This report illustrates the feasibility of percutaneous

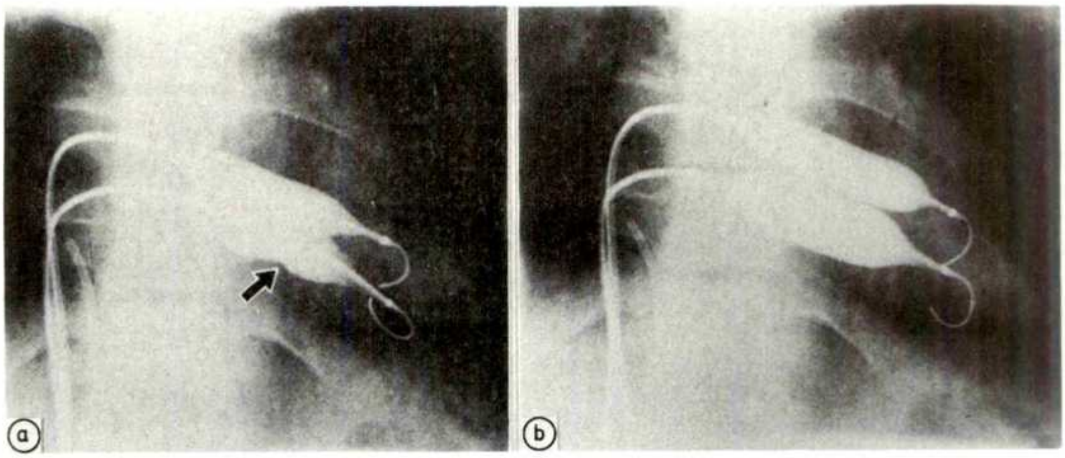

Fig 2 *Two balloons positioned across the tricuspid valve. (a) Balloon indentation (arrow) during early inflation. (b) Loss of balloon indentation after successful double balloon tricuspid valvotomy.*

balloon valvotomy of the stenotic tricuspid valve. With the double balloon technique we achieved a considerable reduction in tricuspid valve gradient together with an increase in valve area, without inducing further tricuspid regurgitation. Precise measurement of small pressure gradients is required for the haemodynamic diagnosis of tricuspid valve stenosis.[5] Hence our strict technique for the gradient measurement includes a second set of simultaneous right atrial pressure recordings, to ensure accuracy by establishing that no calibration drift has occurred, and the maintenance of a relatively constant heart rate with propranolol.

Because of the size of the tricuspid valve, a double balloon technique was required. Our current experience of 25 successful percutaneous mitral valvotomies[4] indicated that an adequate systolic blood pressure would be maintained during prolonged balloon inflation with the double balloon technique, and this proved to be so.

Because the thin leaflets of the tricuspid valve are easily damaged we initially used two 15 mm diameter balloons. These were not successful, however. Successful valvotomy, with the disappearance of indentation, was achieved only when one of the 15 mm balloons was replaced by a 20 mm balloon.

Because tricuspid stenosis and mitral stenosis can occur together, and in view of the recent demonstration of successful double balloon mitral valvotomy,[4] this technique could be applied concurrently to both stenotic valves.

We thank Dr William Sawyer for assistance with preparation of the manuscript and the medical illustration department for their contribution.

References

1 Kan JS, White RI, Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary valve stenosis. *N Engl J Med* 1982;**307**:540–2.

2 Lababidi Z, Jiunn-Ren WU, Walls JT. Percutaneous balloon aortic valvuloplasty: results in 23 patients. *Am J Cardiol* 1984;**53**:194–7.

3 Ionue K, Owani T, Nakamura T, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;**87**:394–402.

4 Al Zaibag M, Ribeiro PA, Al Kasab S, Al Fagih MR. Percutaneous double-balloon mitral valvotomy for rheumatic mitral stenosis. *Lancet* 1986;**i**:757–61.

5 Ockene IS. Tricuspid valve disease. In: Dalen JE, Alpert JS, eds. *Valvular heart disease*. Boston: Little, Brown, 1981:281–328.

Br Heart J 1987;57:54–7

Pericardial constriction caused by primary mesothelioma

MICHAEL J LLEWELLYN, MARK W ATKINSON, BRIAN FABRI

From the Regional Adult Cardiothoracic Unit, Broadgreen Hosital, Liverpool

SUMMARY Primary pericardial mesothelioma is an extremely rare tumour. This case illustrates the typical late presentation with symptoms and signs of constrictive pericarditis. An unusual feature was complete encasement of the heart by tumour. No satisfactory treatment is available.

Case report

A 69 year old retired seaman gave a two month history of progressively worsening breathlessness and central chest discomfort on effort. There was associated weight loss, anorexia, night sweats, and pronounced peripheral oedema. Symptoms were partly relieved by diuretics and vasodilators.

Previous illnesses included longstanding, but well controlled, hypertension (treated with atenolol and hydralazine) and resection of an enlarged prostate two years before presentation, in which histological examination showed foci of well differentiated prostatic adenocarcinoma.

On examination he was unwell, slightly jaundiced, and dyspnoeic at rest. The pulse was regular and of small volume, and the blood pressure was 90/60 mm Hg. The jugular venous pulse was elevated to the angle of the jaw, with sharp "y" descent and there was pitting oedema up to the knees. The cardiac apex was impalpable and the heart sounds quiet without added sounds or murmurs. The lungs were moderately congested with a small right pleural effusion.

A chest radiograph showed cardiac enlargement (cardiothoracic ratio 58%), pulmonary venous congestion, linear collapse, and bilateral pleural effusions. No pleural plaques or lung tumour were seen. The electrocardiogram showed low voltage QRS complexes with non-specific T wave changes. Echocardiography demonstrated thickened pericardium with small anterior and posterior pericardial effusions, normal valves without vegetations, and satisfactory ventricular contractility.

Initial investigation showed: haemoglobin 12·8 g/dl; white cell count 10·8 × 10^9/l; sodium 128 mmol/l; urea 21·7 mmol/l; creatinine 211 mmol/l; concentrations of liver transaminases were slightly raised; lactate dehydrogenase 189 U/l (normal 80–160 U/l); alkaline phosphatase 133 U/l. Blood, sputum, and urine culture were sterile. Viral titres, tuberculin test, and autoantibody screen were negative. Acid phosphatase concentration was not raised. Pleural aspiration drew clear yellow fluid, protein content 35 g/l; cytology showed mesothelial cells.

At cardiac catheterisation diastolic pressures in all chambers were almost equal (right atrium mean 22; right ventricle 40/22; pulmonary artery 45/30; mean pulmonary capillary wedge 24; left ventricle 100/22; aorta 100/80 mm Hg.) Cineangiography showed small and well contracting left and right ventricles with considerable limitation of diastolic filling. Coronary arteriography showed a 75% proximal stenosis of the anterior descending branch of the left coronary artery.

At thoractomy the heart was found to be surrounded by thick white tumour masses, which had spread to the adjacent mediastinal nodes and pleura. Resection was impossible and the patient died several hours after return from the operating theatre.

At postmortem the whole heart was found to be encased by tumour, with pericardium adherent to the epicardium forming a continuous band of white tissue 1 cm thick (fig 1). Several nodules of tumour surrounded the great vessels and the heart plus tumour weighed over 1 kg. Numerous small pleural nodules of tumour were present, and none was

Requests for reprints to Dr Michael J Llewellyn, Regional Adult Cardiothoracic Unit, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB.

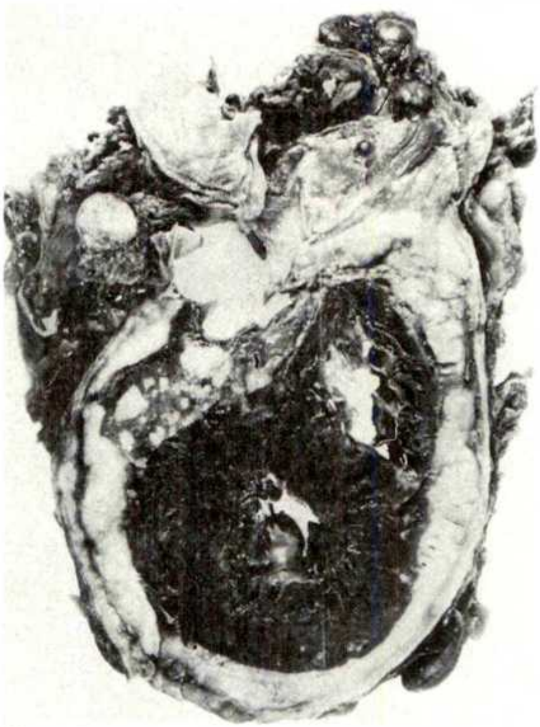

Fig 1 *Transverse section of heart and great vessels showing complete encasement of heart by tumour.*

larger than 1 cm in diameter. There was no evidence of residual prostatic tumour or of any pelvic or abdominal neoplasia or lymphadenopathy.

The histological appearances of most of the pericardial tumour indicated an anaplastic carcinoma that had infiltrated the myocardium (fig 2). There were, however, numerous areas showing papillary differentiation (fig 3a), acinar elements (fig 3b), mesothelial differentiation (fig 3c), and frankly sarcomatous differentiation (fig 3d). Neutral mucin stains (periodic acid Schiff diastase) and immunoperoxidase stains for prostatic acid phosphatase, prostatic specific antigen, and carcinoembryonic antigen were negative. These features meet the diagnostic criteria for malignant mesothelioma.[1]

Discussion

Primary tumours of the pericardium are extremely rare; one of the largest necropsy series of recent years gives an incidence of 0·0022% in 500 000 cases.[2] Mesothelioma is probably the commonest type, followed by sarcoma, teratoma, fibroma, lipoma, and angioma.[3] The incidence in both sexes is almost equal, with an age range of 1–79 years.

The tumour is commonly diagnosed at a late stage and often results in evidence of constriction caused by tumour expansion or associated serous or haemorrhagic pericardial effusion. The diagnosis in this case was suspected because of thickened pericardium seen on the echocardiogram; and in view of the previous history of malignancy, a secondary rather than primary tumour seemed more likely. Although cardiac catheterisation can confirm pericardial constriction and indicates ventricular function, definitive diagnosis is often not made until thoractomy. The pleural exudate obtained in this case contained non-specific mesothelial cells and was clearly a pointer to the tumour. Pericardial aspiration was not attempted before operation but would probably have produced a dry tap, perhaps a helpful feature in differential diagnosis.

Radioisotope scanning with gallium or technetium may be used to detect malignant pericardial effusion but results are not regarded as being highly specific.[3] Computed tomography may well be helpful in distinguishing tumour from fluid in the pericardial space.[4]

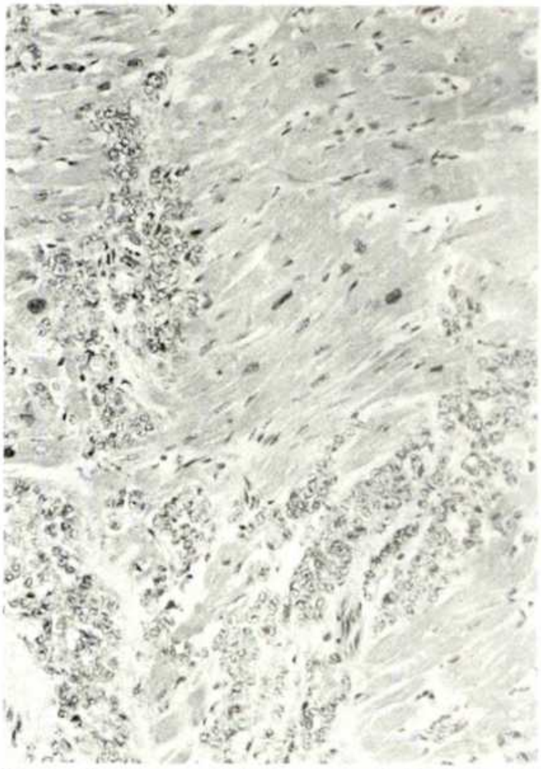

Fig 2 *Photomicrograph showing myocardial infiltration by tumour.*

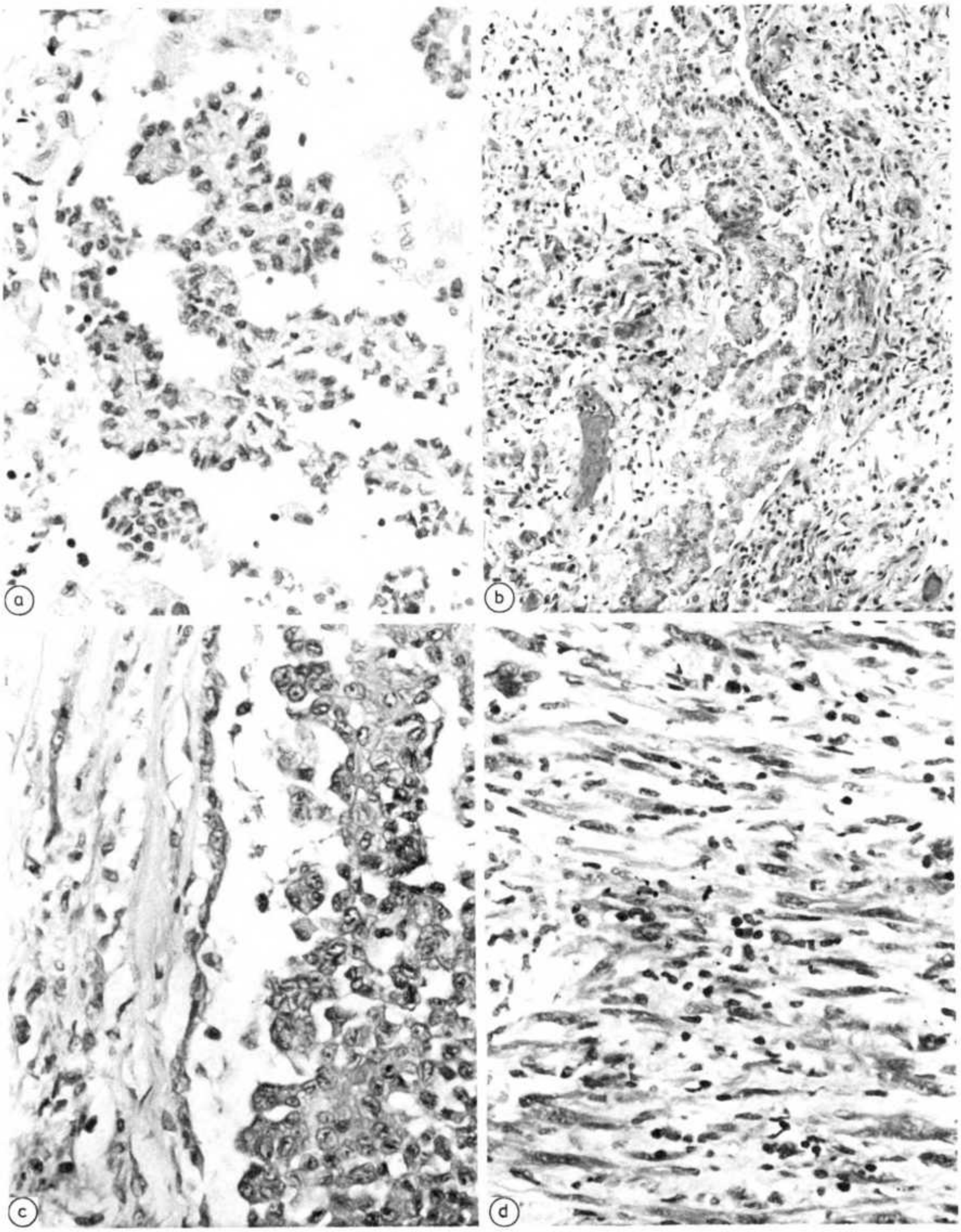

Fig 3 *Photomicrographs (a) papillary elements, (b) acinar elements, and showing (c) mesothelial and (d) sarcomatous differentiation.*

The gross pathological appearance may be of a localised mass, solid or cystic or angiomatous, or of diffuse nodules. Complete encasement of the heart by tumour is an unusual feature and has been rarely reported.[4-8] The pericardial tumour is often adherent to or may invade the myocardium.[9] The tumour can also invade the conducting tissue or coronary arteries, or compress the great vessels. Local spread is common, but extrathoracic metastasis is extremely rare. In one review stringent criteria were applied to the diagnosis of mesothelioma when the pericardium was the postulated primary site,[10] particularly when numerous pleural metastases were present. The clinical presentation and pathological distribution of tumour must, therefore, be considered together when deciding on the diagnosis and primary site. Histological differentiation is often difficult because of the pleomorphic nature of the tumour.

Possibilities for treatment are usually limited by late detection. Complete tumour resection is virtually impossible so operation is usually confined to attempts to relieve obstruction. The results of systemic chemotherapy are disappointing; but if associated pericardial effusion is present local instillation of cytotoxic drugs or sclerosing agents can be helpful. Radiotherapy may temporarily reduce the size of the tumour.

There has been no clear association between asbestos exposure and pericardial mesothelioma. This is probably because the paucity of recorded cases has not allowed an adequate epidemiological study. As in many cases, this diagnosis was made after death and the relevant history was not available.

We thank Dr R G Charles and Mr J B Meade for permission to report this case and Dr W Kenyon and Dr F Whitwell for their help with histological assessment.

References

1 Jones JSP, Lund C, Plantey HT. *Colour atlas of mesothelioma.* Lancaster: MTP Press, 1985:15–6.
2 Cohen JL. Neoplastic pericarditis. *Cardiovasc Clin* 1976;7:257–69.
3 Darsee JR, Braunwald E. Diseases of the pericardium. In: Braunwald E, ed. *Heart disease, a textbook of cardiovascular medicine.* Philadelphia, London, Toronto: WB Saunders, 1980:1563.
4 Yilling FP, Schlant RC, Hertzler GL, Krzyniak R. Pericardial mesothelioma. *Chest* 1982;**81**:520–3.
5 Pietra GG, Silber E, Levin B, Pick A. Clinical pathologic conference. *Am Heart J* 1968;75:545–58.
6 Elguezabal A, Parry JP, Depace NL. Massive metastatic cardiac tumour encasement with pericardial constriction. *J Med Soc NJ* 1980;77:820–4.
7 Miscia VF, Holsinger JW, Mathers DH, Eliot RS. Primary pericardial tumour masquerading as constrictive pericarditis. *JAMA* 1974;**230**:722.
8 Kirwan M, Blake S, Neligan M, *et al.* Cardiac constriction due to malignant disease of the pericardium. *Ir J Med Sci* 1983;**152**:454–5.
9 Sytman AL, Macalpin RN. Primary pericardial mesothelioma: report of two cases and review of the literature. *Am Heart J* 1971;**81**:760–9.
10 Anderson JA, Hansen BF. Primary pericardial mesothelioma. *Dan Med Bull* 1974;**21**:195–200.

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Successful treatment by doxycycline of endocarditis caused by ornithosis

L J E WALKER, A A J ADGEY

From the Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, Northern Ireland

SUMMARY The case of a 59 year old man with ornithosis endocarditis and a history of contact with pheasants is reported. Treatment with oxytetracycline was not tolerated and so doxycycline was substituted. Over the two year follow up the patient's clinical condition and serial echocardiographic appearances improved and *Chlamydia psittaci* complement fixation titres returned to normal. Valve replacement was not required.

Case report

A 59 year old security officer was admitted to hospital in Londonderry, on 4 August 1983. He gave a six month history of loss of energy, anorexia, excessive sweating, non-productive cough, mild shortness of breath, and weight loss of 16 kg. Early on in the illness, he had noticed headaches in the morning. There was no previous cardiac history. Medication on admission was oral iron. He had not received antibiotics.

He kept chickens, which appeared to be healthy. He had not been in contact with budgerigars, turkeys, pigeons, parakeets, or cats.

He was thin on admission, with a temperature of 100°F (37·75°C). Early finger clubbing was present, but there were no petechiae or splinter haemorrhages. There was no lymphadenopathy. A grade 3/6 apical systolic murmur radiating to the axilla and a grade 1/6 early diastolic murmur along the left parasternal edge were heard. Chest was clinically clear. The spleen was enlarged (3 fingerbreadths) but the liver was not. Fundoscopy was normal.

The initial haemoglobin concentration (10 g/dl) and red cell indices, and white cell, platelet and reticulocyte counts were normal. The erythrocyte sedimentation rate was > 150 mm/h. Blood urea and electrolyte concentrations and liver function tests were normal. Six blood cultures showed no growth. Gammaglobulin was 50 g/l (normal range 7–15 g/l), C3 complement 0·42 g/l (normal range 0·5–1·2 g/l), and C4 0·18 g/l (normal range 0·2–0·5 g/l). Circulating immune complexes were not detected. Urine microscopy showed no red cells and a chest *x* ray indicated slight cardiomegaly. Electrocardiogram showed mild left ventricular hypertrophy on voltage criteria. Serological testing for Q fever, *Brucella, Mycoplasma pneumoniae,* and the Paul-Bunnell reaction were negative. The *Chlamydia psittaci* complement fixation titre was 1:160. M mode echocardiography showed a vegetation on the mitral valve.

Culture negative endocarditis was diagnosed. Intravenous benzylpenicillin (16 megaunits) and gentamicin (240 mg) given daily in divided doses were started on the second day of admission. After this treatment the patient felt better and there was no fever. Splenomegaly diminished rapidly.

On the tenth day of admission the patient was transferred to our centre. Cross sectional echocardiography confirmed a vegetation on the mitral valve. There was moderate mitral and aortic incompetence. The non-coronary cusp of the aortic valve, which was tricuspid, appeared to be partially disrupted.

After three weeks, penicillin treatment was withdrawn because severe neutropenia developed. The white cell count recovered rapidly after withdrawal of the drug. Vancomycin was substituted and gentamicin was continued. Six weeks after his initial admission to hospital the *Chlamydia psittaci* complement fixation titre was 1:1280 and oxytetracycline (250 mg orally four times a day) was started. Vancomycin (which he had been given for three weeks) and gentamicin (for six weeks) were discontinued.

Further questioning at this stage revealed a new

Requests for reprints to Dr L J E Walker, Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast BT12 6BA, Northern Ireland

possible source of infection—his son's pheasants. The patient, who was responsible for feeding them, had noticed that two of them had been unwell and that they were "shedding feathers". Six months before admission he had injured the palm of his right hand on the barbed wire fence enclosing the pheasants. The pain caused by the injury was so severe that he was unable to use his hand for three days.

Because oxytetracycline caused nausea and vomiting in this patient we treated him with doxycycline (200 mg orally daily), which was well tolerated. Treatment was continued for two years, and during this time he gained weight, and the haemoglobin, erythrocyte sedimentation rate, and high γ globulin concentration became normal. The *Chlamydia psittaci* complement fixation titre reverted to 1:160. Serial echocardiography (fig a and b) showed that the vegetation on the mitral valve became smaller. Moderate mitral and aortic incompetence persist.

Disposal of the birds by the patient's family was unsatisfactory; the chickens were sold and the pheasants were set free.

Discussion

Endocarditis caused by *Chlamydia* is rare. In a recent review of 544 episodes of infective endocarditis in 541 patients Bayliss *et al* reported negative blood cultures in 53 cases.[1] *Chlamydia* was only implicated in one case. In an earlier review by Pesanti and Smith of 52 cases of culture negative endocarditis, *Chlamydia* was not mentioned.[2] We have found nine published reports of *Chlamydia psittaci* throughout the world.[3-9] Of these six survived. Three of these owed their survival to valve replacement.[3 4 9] The only patient in whom medical treatment alone was successful was described by Jariwalla *et al*.[7] In their patient tetracycline treatment failed but rifampicin was successful.

Most patients had been in contact with birds—budgerigars, parrots, canaries, and pigeons seemed to be the main sources of infection. In 1967 Meyer reviewed the host range of *Chlamydia* and tabulated about 130 species of birds known to harbour *Chlamydia*.[10] Other animals, including the domestic cat, can spread the disease. Regan *et al* reported infective endocarditis with glomerulonephritis associated with *Chlamydia psittaci* infection of a cat.[11] In our patient the birds that appeared to have been infected were the pheasants. Nevertheless, apparently healthy chickens can harbour the organism. We could not confirm the source of infection, because all of the birds had been disposed of; unfortunately they were not destroyed as has been recommended.[12]

On at least three occasions our patient had been questioned closely about avian contact. The fact that

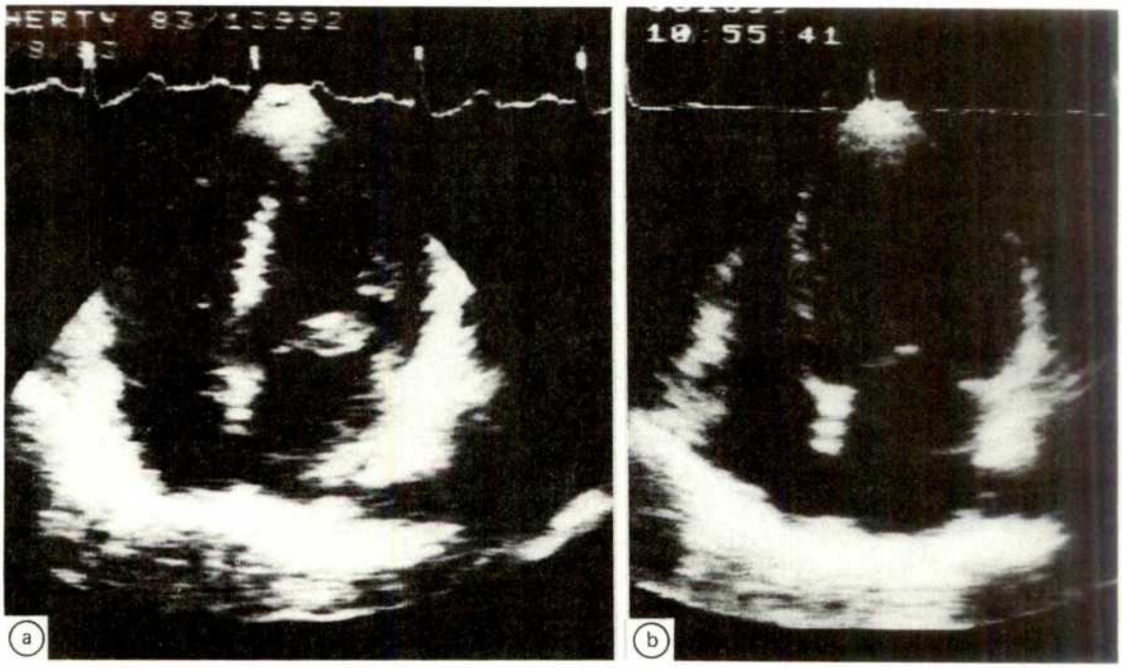

Figure *Cross sectional echocardiograms of a four chamber view obtained in September 1983 (a) and showing a vegetation on the mitral valve and (b) in August 1985. The size of the vegetation on the mitral valve is considerably reduced in (b).*

the most relevant part of the history only emerged after repeated questioning is in keeping with the experience of others, who have found that a history of exposure to birds is often only obtained after repeated questioning.

This patient is unusual in that pneumonitis did not appear as a major complication, nor was it the reason for presentation.[13] Cardiac complications of chlamydial infection include myocarditis,[14 15] pericarditis,[16] and endocarditis.[3-9] In addition, Ward and Ward have suggested a link between chronic infection and acquired valve disease.[17] Embolic phenomena have been described,[5] but were not a feature in this case.

The initial good response to benzylpenicillin and gentamicin treatment was undoubtedly due to the penicillin; however, many workers have observed penicillin treatment failures. The aminoglycosides have no demonstrable activity against the organism.[10] There is another published report of successful medical treatment with doxycycline; however, the patient died a month after double valve replacement that was carried out approximately two years after the initial presentation.[11] Because *Chlamydia psittaci* is an intracellular organism,[16] and tetra-cycline is only a static agent the patient is being kept under close review in case the need for long term doxycycline treatment or valve replacement or both arises. Oakley has suggested that valve replacement should be carried out in most cases.[18] After two years' follow up, the *Chlamydia psittaci* complement fixation titre in our patient remains at 1:160. Valve replacement has not been necessary.

References

1 Bayliss R, Clarke C, Oakley CM, Somerville W, Whitfield AGW, Young SEJ. The microbiology and pathogenesis of infective endocarditis. *Br Heart J* 1983;**50**:513–9.
2 Pesanti EL, Smith IM. Infective endocarditis with negative blood cultures. An analysis of 52 cases. *Am J Med* 1979;**66**:43–50.
3 Ward C, Sagar HJ, Cooper D, Ward AM. Insidious endocarditis caused by *Chlamydia psittaci*. *Br Med J* 1975;**iv**:734–5.
4 Birkhead JS, Apostolov K. Endocarditis caused by a psittacosis agent. *Br Heart J* 1974;**36**:728–31.
5 Bromage D, Jeffries DJ, Philip G. Embolic phenomena in chlamydial infection. *Journal of Infection* 1980; 2:151–9.
6 Levison DA, Guthrie W, Ward C, Green DM, Robertson PGC. Infective endocarditis as part of psittacosis. *Lancet* 1971·**ii**:844–7.
7 Jariwalla AG, Davies BH, White J. Infective endocarditis complicating psittacosis· response to rifampicin. *Br Med J* 1980;**280**·155.
8 Grist NR, McLean C Infections by organisms of *Psittacosis/Lymphogranuloma venereum* group in the West of Scotland. *Br Med J* 1964;**ii**:21–5.
9 Jones RB, Priest JB, Kuo CC. Subacute chlamydial endocarditis. *JAMA* 1982;**247**:655–8.
10 Schachter J, Dawson CR. Psittacosis. In: *Human chlamydial infections*. Littleton, Massachusetts: PSG Publishing Company, 1978.9–43.
11 Regan RJ, Dathan JRE, Treharne JD. Infective endocarditis with glomerulonephritis associated with cat chlamydia (*C psittaci*) infection. *Br Heart J* 1979;**42**:349–52.
12 Macfarlane JT, Macrae AD. Psittacosis. *Br Med Bull* 1983;**39**:163–7
13 Murray HW, Tuazon C. Psittacosis. *Med Clin N Am* 1980;**64**.515–9.
14 Coll R, Horner I. Cardiac involvement in psittacosis *Br Med J* 1967;**4**:35–6
15 Dymock IW, Lawson JM, MacLennan WJ, Ross CAC. Myocarditis associated with psittacosis. *Br J Clin Pract* 1971;**25**·240–2.
16 Isaacs D. Psittacosis. *Br Med J* 1984;**289**:510–1.
17 Ward C, Ward AM. Acquired valvular heart-disease in patients who keep pet birds. *Lancet* 1974;**ii**:734–6.
18 Oakley CM. Infective endocarditis. *Br J Hosp Med* 1980;**24**:232–43.

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Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held at the Wembley Conference Centre, London, on Tuesday to Thursday, 25 to 27 November 1986. The President, D G JULIAN, took the Chair during private business. The scientific sessions were under the chairmanship of P HARRIS.

Abstracts of papers

Medial and endothelial functional integrity during preparation of autologous human saphenous vein for coronary artery bypass grafting

G D Angelini
Department of Cardiac Surgery, University Hospital of Wales, Cardiff, and Department of Cardiology, University of Wales College of Medicine, Heath Park, Cardiff

Inadvertent medial and endothelial damage caused during surgical preparation may contribute to subsequent vein graft occlusion. Measurements of ATP concentration and ATP:ADP ratio provided quantitative markers for medial integrity and of stimulated prostacyclin production for endothelial function. ATP concentration was reduced from 480 (30) ($n = 28$) to 260 (40) nmol/g wet weight ($n = 15$) and ATP:ADP ratio from 2·4(0·1) to 1·3(0·1) during surgical preparation in which patient's heparinised arterial blood was used for distension and peroperative storage. ATP concentration was significantly lower (170 (20) nmol/g wet weight, $n = 13$, $p < 0·05$) when distension pressure was not limited to 300 mm Hg. Experimental distension but not storage reproduced these effects of surgical preparation. Surgical preparation also reduced the rate of stimulated prostacyclin production from 9 (1) ($n = 36$) to 5·5 (0·6) pg/min/mg wet weight ($n = 22$). Neither distension nor storage was responsible for the reduction, which appeared to be the result of endothelial fragility under surgical manipulation. A morphometric technique showed that surgically prepared veins had only 45 (7) % of their intimal surface covered with an intact endothelium. After surgery preparation ($n = 12$) by means of a procedure that used first proximal anastomosis and distension of the vein by the patient's own arterial pressure, ATP concentration (480 (70) nmol/g wet weight), ATP:ADP ratio (2·4 (0·1)), and prostacyclin production (10 (2) pg/min wet weight) were indistinguishable from values in freshly isolated vein.

The patency rate of vein grafts with an intact media and endothelium must now be investigated.

Ambulatory pulmonary artery pressure monitoring in the investigation of myocardial ischaemia

R D Levy
National Heart Hospital, London

A new method for the measurement of ambulatory pulmonary artery diastolic pressure by a transducer-tipped catheter and a simple recording system has been developed and applied to study changes in left ventricular filling pressure during myocardial ischaemia. Changes in pulmonary artery diastolic pressure and the ST segment of a frequency modulated electrocardiogram were assessed on a beat to beat basis in 19 patients with coronary artery disease; six patients with syndrome X and six subjects acted as controls. During exercise, pulmonary artery diastolic pressure increased in patients with coronary artery disease; episodes of painful and painless ST segment depression during ambulatory monitoring were accompanied by similar rises in pulmonary artery diastolic pressure. There was no increase in pulmonary artery diastolic pressure during exercise or ambulatory monitoring in controls or patients with syndrome X. All groups, including controls, showed a significant rise in pulmonary artery diastolic pressure at night and this may be of importance in reducing the threshold for nocturnal myocardial ischaemia.

Thus ambulatory pulmonary artery pressure monitoring has permitted the haemodynamic significance of ST segment changes during myocardial ischaemia to be evaluated in ambulant patients.

Cardiac pumping capability and prognosis in heart failure

L B Tan
Department of Cardiovascular Medicine,
East Birmingham Hospital

When the maximum pumping performance of a failing heart cannot exceed the resting level of normal individuals (whose average cardiac power output is 1·1 W), the prognosis can be regarded as grave This hypothesis was tested in 63 patients with severe acute and chronic heart failure (New York Heart Association class III or IV; left ventricular ejection fraction 24·2 (10·0) %). Haemodynamic measurements were made by means of thermodilution Swan-Ganz catheters and arterial cannulas. The maximum cardiac performance was determined by calculating the maximum hydraulic power output achieved by the heart during incremental dobutamine infusion, and the patients were prospectively followed up for one year. Twenty two patients had maximum power output (W_{max}) < 1·1 W and all but three of them died (of terminal heart failure) within one year. Forty one patients had W_{max} > 1·1 W; 37 of them survived for more than one year and four died suddenly. In the subgroup of 27 patients who had cardiogenic shock at the time of investigation, all (n = 17) who had W_{max} < 1·1 W died within the follow up period.

In conclusion, the results of this prospective study showed that hydraulic power output is a meaningful measure of cardiac pumping performance, and that the mechanical state of the heart is incompatible with prolonged survival if its maximum power output is less than the normal resting value.

Is there an optimum waveform for cardiac defibrillation?

C M Wilson
Royal Victoria Hospital, Belfast

One, five, or 10 transthoracic shocks (400 J stored energy) were applied to anaesthetised greyhounds. Twenty dogs died during the experiment (1 shock, 0/6; 5 shocks, 8/18; 10 shocks, 12/17). There was little damage in the 1 shock group at 3 days (0·01 (SEM) 0·01 g). The survivors in the five and 10 shock groups had significant ST segment elevation at 15 min and macroscopic cardiac damage at 3 days (5 shock, 7·2 (2) g and 10 shocks 13·1 (1·8) g, $p < 0{\cdot}05$). The defibrillation threshold of five waveforms was compared in eight dogs (Lown, Belfast, Edmark sine waves, and 5 and 20 ms trapezoid waves). The threshold currents of the three sine waves and 5 ms trapezoid were not significantly different (Lown 12·2 (1·2) A, Edmark 14·7 (0·9) A, Belfast 15·7 (1·1) A, 5 ms 12·2 (1·3) A). The 20 ms threshold (9·0 (1·1) A) was significantly less than that of the Belfast and Edmark sine waves ($p < 0{\cdot}01$). The damage caused by these five waveforms was assessed at 3 days in the 36 survivors out of 49 dogs (no shocks (6 dogs) or 5 shocks (400 J for sine waves: capacitor voltage 1100 V for trapezoidal waveforms)). The Belfast (21·9 (2·9) g) and Edmark (16·0 (3·7) g) sine wave caused significantly more damage than the Lown sine wave (3·5 (1·3) g) ($p < 0{\cdot}01$). The 20 ms trapezoid waveform (8·1 (3·1) g) caused more damage than the 5 ms waveform (0·7 (0·3) gm) ($p < 0{\cdot}05$).

Increasing numbers of high energy shocks are associated with increasing mortality and cardiac damage. Different waveforms differ in their potential to cause injury in this model.

Results from surgical treatment for ventricular tachycardia and fibrillation

A W Nathan, S R Large, D W Davies, C P Young,
A J Camm, S J Edmondson, G M Rees,
R A J Spurrell
St Bartholomew's Hospital, London

Since 1977, 54 patients aged 16–75 (mean 55) years have undergone operation for ventricular arrhythmias. Fifty two presented with ventricular tachycardia (nine of these also had ventricular fibrillation) and two presented with ventricular fibrillation alone. The aetiology was thought to be ischaemic in 45 (usually with poor left ventricular function), two had right ventricular dysplasia, two had coronary muscle bridges, one had global cardiomyopathy, one had mitral prolapse, one was post-Fallot's repair, and two had no other detectable heart disease. Antiarrhythmic procedures (multiple in some cases) included endocardial resection in 35, aneurysmal/myocardial resection in 31, cryoablation in 14, ventriculotomy in seven (encircling in two), and coronary grafting alone in two. Coronary grafting was performed as an additional procedure in 23, mitral replacement in two, division of a muscle bridge in two, and repair of a ventricular septal defect in one. Implantable defibrillator patches were placed in two. Fifty two (96%) patients survived operation but an additional 10 died before discharge, giving a total mortality of 12 (22%) patients. At discharge 28 (52%) patients were totally arrhythmia-free without medical treatment and 12 (22%) were arrhythmia-free with medical treatment (previously ineffective), giving a total of 40 (74%) patients completely controlled. The first and second halves of the group were compared. Overall mortality fell from 30% to 15%, while the success rate without medical treatment rose from 37% to 67% and overall success rose from 67% to 81%.

Operation for ventricular arrhythmias is highly effective despite the generally poor myocardial function of this patient group. Increasing experience, with better mapping and surgical techniques, has improved both the success rate and survival.

Prevention of sudden death: two years' experience with the implantable defibrillator

P Holt, J C P Crick, E Sowton
Guy's Hospital, London

The automatic implantable cardioverter defibrillator offers long term protection against sudden death in patients with paroxysmal ventricular tachycardia (VT) and ventricular fibrillation (VF). We report our two year experience with this device. Four automatic implantable defibrillators model B (AID-B) were used in three patients. There were two men and one woman aged 76, 50, and 49 years. One had ischaemic heart disease and two had cardiomyopathies. All had documented recurrent episodes of VT and VF producing syncope and requiring cardioversion. These arrhythmias occurred despite antiarrhythmic drugs. After a median sternotomy two screw-in electrodes and two patches were sutured to the ventricular epicardium. The former were used for sensing and the latter for defibrillation. During the operation VF/VF was induced in all patients and the patch positions were adjusted to produce a defibrillation threshold of 15 J or less. The AID-B unit was positioned in a pocket on the upper abdominal wall. There were no complications. The 50 year old man also had an antitachycardia pacemaker (Tachylog) implanted to terminate VT. The AID-B device was implanted as back-up should accleration of the VT occur. Follow up ranges from 5 to 24 months. The AID-B has successfully defibrillated two episodes of VF in one patient. In the second patient the Tachylog has terminated 50 attempts of VT and the defibrillator six episodes of VF. The woman has had only short runs of VT which have not yet required defibrillation. Premature failure of the device at 19 months occurred in one patient, and inappropriate defibrillation occurred immediately after operation in another. This was due to uncontrolled AF. All patients are now well and active.

Thus the AID-B is safe and effective in the treatment of patients with VT/VF.

Surgical management of ventricular arrhythmias within two months of myocardial infarction

J Bourke, Suda Tansuphaswadikul, J C Cowan, C J Hilton, R W F Campbell
Freeman Hospital, Newcastle upon Tyne

Patients with medically refractory sustained ventricular tachycardia (VT) and recurrent ventricular fibrillation (VF) complicating the late hospital phase of myocardial infarction have a very poor prognosis. Thirteen such patients aged 40–68 years underwent arrhythmia surgery within two months of anterior myocardial infarction (three patients within four weeks). Nine had uniform VT, three had multiform VT/VF, all had required DC cardioversions, and all had failed multiple drug tests (mean 4·5) including amiodarone in 10 patients. In 12 patients left ventricular function was poor: mean ejection fraction was 21% (range 14–31%) and mean end diastolic pressure 21 mm Hg (range 14–30 mm Hg). One patient had normal left ventricular function with an ejection fraction of 47%. Surgery was based on epi/endocardial activation mapping in VT and fragmentation mapping in sinus rhythm (abnormal electrograms defined as >100 ms duration). VT was "macro" reentrant in three patients. All electrically abnormal left ventricular endocardium was resected in 13 patients, with additional right ventricular resections in one and cryoablations in two. Coronary artery grafting was performed in six patients, aneurysmectomy in nine, and mitral valve replacement in one. The perioperative mortality was 30·8% (four of 13 patients). All died of pump failure. Death was unrelated to time from infarction (4, 5, 6, and 8 weeks), ejection fraction (17%, 20%, 27%, and 25%), and VT type. In the nine survivors there have been no late deaths or arrhythmia recurrences (median follow up 14 months). None is on antiarrhythmic drugs.

Surgical treatment of medically refractory ventricular arrhythmias carries a high operative mortality but is an effective management strategy even in patients with severely impaired left ventricular function.

Antitachycardia pacing: use of the Intermedics Intertach with a temporary electrode for ambulatory electrophysiological studies and assessment before permanent implantation

J E Sanderson, R B G Palmer, B Y Wright
Department of Cardiology, Taunton and Somerset Hospital, Musgrove Park Branch, Taunton, Somerset

The results from electrophysiological studies (EPS) done in the laboratory can be misleading because of changes in autonomic tone. Therefore for assessment of patients before implantation of antitachycardia pacemakers we have devised a system that uses an Intermedics Intertach pacemaker with a temporary atrial electrode for the proper assessment of the best termination program during normal ambulatory conditions for up to one week. To date three patients (ages 27, 24, and 57) have been studied in this way. They were considered for antitachycardia pacing because of recurrent symptomatic tachycardias unresponsive to the usual drugs (including amiodarone) or because of side effects. A short EPS study was done to confirm the diagnosis of reciprocating atrioventricular (AV) nodal tachycardias that would terminate with extra stimuli and to ensure that there was not an AV bypass tract that would conduct at high rates during atrial fibrillation. A transvenous temporary atrial electrode was left in situ and connected externally to an Intermedics Intertach (model 262–12) in a box that was attached to the patient. In this way we were able to study many different programs, starting and terminating the tachycardia at will under all normal ambulatory conditions including during treadmill exercise testing. When we were satisfied that the tachycardias could be properly controlled under all conditions, a permanent Intermedics Intertach pacemaker was implanted in the usual way (on the other side). In all three patients the control of the tachycardias has been excellent.

We suggest therefore that a trial period with an external Intertach pacemaker is the best form of EPS for these patients, so that the termination programs can be checked under normal conditions.

Low energy ablation of atrioventricular conduction: comparison with conventional ablation

A D Cunningham, E Rowland, A F Rickards
National Heart Hospital, London

Ablation of atrioventricular (AV) conduction by catheter electrodes has become an accepted method for the treatment of refractory supraventricular arrhythmias. We used a conventional high energy defibrillator (group A, six patients) and subsequently used a modified low energy delivery system which optimises peak delivered current while reducing delivered energy (group B, four patients). In Group C (two patients) both techniques were attempted. Conventional electrode catheters were used in all patients. Ten patients had paroxysmal or established atrial flutter or fibrillation and two had permanent junctional reentry tachycardia. In group A (all male; aged 38–68 (mean 54)) a low energy (10–20 J) shock was delivered to demonstrate transient interruption of AV conduction and was followed by definitive shocks of 320 J. Two patients each underwent two procedures. After follow up of 22–28 months (mean 25) complete heart block has persisted in five, but in one patient conduction returned. Total delivered energy was 340–1280 J (mean 711 J). In group B (2 men, 2 women; ages 55–68 (mean 62)) initial low energy shocks ranged from 0·5–2 J. Definitive shocks ranged from 3 to 37 J. One patient required a second procedure. Persistent complete heart block was achieved in three (follow up 7–11 months) patients; in the remaining patient AV conduction returned after three months, but symptoms are controlled by previously ineffective drugs. Total energy in group B patients was 3·6–39·7 J (mean 20·2 J). In group C (one man, one woman; aged 61 and 45) attempts with conventional ablation techniques (total energy 350 J and 1000 J) failed to produce permanent complete heart block; low energy ablation (maximum 40 J, total energy 118 J and 182 J) also failed.

Thus low energy ablation may be achieved with greater than tenfold decrease in delivered energy without compromising the success of the technique.

The role of electrode geometry in successful low energy ablation

P Holt, E Boyd
Departments of Cardiology and Clinical Physics and Bioengineering, Guy's Hospital, London

We investigated the effects of varying energies used by electrodes of different geometry in order to reduce energy requirements for endocardial ablation. Tank, gel, and animal studies were performed before clinical use. From initial experiments with eight leads three electrodes were chosen; there were the 6F bipolar USCI, the Vitatron helifix, and Sorin S90. They were studied in eight adult mongrel dogs. The electrode under test was positioned in the right, then left ventricle, and energy delivered to each in turn. Electrocardiograms and 24 hours tapes were repeated monthly. At five months left ventricular angiograms and endo- and epicardial electrograms were obtained. The energy delivered was 10 J (Sorin), 50 J (Helifix), and 50–400 J (USCI) and energy was delivered as single and multiple impulses (for example 1 × 50 J and 5 × 10 J). Acute complications included sudden death and arrhythmias. These were related to high energies, multiple shocks, and the USCI electrode. In the long term thin walled aneurysm was produced in one dog who had 50 J via a USCI catheter. The size of the endocardial lesions at five months ranged from 8 × 5 mm to 30 × 35 mm and lesions were largest with 50 J via the Helifix electrode. The Sorin S90 (10 J impulses) produced well localised lesions at 5 months that were 5–10 mm in diameter. Fewer complications occurred with this electrode and it was chosen for clinical trial.

It has subsequently been used in His bundle ablation in two male patients with paroxysmal atrial fibrillation. Successful ablation of conduction was safely achieved by a single shock of 10 J.

Magnetic resonance imaging of pulmonary arteries and their systemic connections in pulmonary atresia

R S O Rees, Jane Somerville, S R Underwood,
D N Firmin, R H Klipstein, D B Longmore
Paediatric and Adolescent Unit, National Heart Hospital, and Magnetic Resonance Unit, National Heart and Chest Hospitals, London

Patients with complex pulmonary atresia require several investigations and operations. The role of magnetic resonance (MR) in assessing the origin and course of systemic collateral arteries, the anatomy of the central pulmonary arteries, and the patency of surgical shunts has been studied with the aim of reducing the need for invasive angiography. Transverse, coronal, and sagittal MR images were obtained in eight adolescent patients and they were assessed without knowledge of surgical and angiographic data. The MR images showed the origin and proximal course of 12 out of 15 large systemic collaterals in six patients. Their full course and distal connections were not seen. The other two patients had no large collaterals on the MR images or at angiography. Central pulmonary artery anatomy varied from full development to complete absence. Transverse slices showed hypoplastic pulmonary arteries particularly well and the MR findings were in close agreement with surgical and angiographic data in all patients. Two surgical shunts were shown to be patent and five occluded at operation and angiography, and this was confirmed on the MR images. The patency of a further four shunts was uncertain, but the MR studies suggested that they were occluded.

MR imaging is capable of providing essential information for the management of pulmonary atresia without the need for invasive investigation.

Coarctation of the aorta: an echocardiographic, anatomical, and functional study

L D Allan, S Chita, R H Anderson, N Fagg,
D C Crawford, M J Tynan
Guy's Hospital and the Cardiothoracic Institute, London

In a study of over 3000 patients by fetal echocardiography the right ventricle was normally seen to be similar in size to the left, and the pulmonary artery was slightly larger than the aorta. In our series 25 patients had normal cardiac connections but right/left ventricular and pulmonary artery/aortic disproportion, with the right side of the heart dilated relative to the left. In 22 cases the disproportion was seen prenatally, in three cases retrospectively. Because this appearance was associated with coarctation of the aorta in an initial case, aortic arch anomaly was strongly suspected in 19 of the 22 cases which were noticed in prenatal life. In the other three cases the ventricular disproportion was thought to be related to the presence of a diaphragmatic hernia. Aortic arch anomaly, coarctation, or interruption was confirmed in 15 of the 19 cases; three fetuses are still in utero. There was one false positive. The coarctation lesion was found anatomically in six cases before 24 weeks' gestation; this refutes the theories that this lesion develops postnatally in association with ductal closure. Aortic blood flow was diminished in 15 cases studied by Doppler. There was, however, a similar reduction in aortic blood flow in the cases of ventricular disproportion related to diaphragmatic hernia This suggests that aortic blood flow per se does not cause the coarctation lesion but occurs as a result of it.

Successful management of refractory supraventricular tachycardia in children with flecainide acetate

Janice Till, D Holt, D Ward, E A Shinebourne
Brompton Hospital and St George's Hospital, London

Thirteen children aged 0·2 to 15 7 (median 7·1) years with supraventricular tachycardia (SVT), unresponsive to a range of antiarrhythmic agents (median 3) were treated with flecainide acetate (FA). Six children had Wolff-Parkinson-White syndrome, three AV nodal reentrant tachycardia, one atrial flutter, one ectopic atrial tachycardia, and in two the mechanism was not established. In 12 of the children FA 2 mg/kg was given over 5–10 minutes during tachycardia. Termination of tachycardia was achieved in 11. In nine of the 10 children with a reentrant arrhythmia termination was in the retrograde limb of the circuit. Side effects were encountered in two. Preliminary studies to evaluate the elimination half life after intravenous administration were performed in five of the children. The half life ranged from 6 9–12 (mean 8·7) hours. This compares with half lives of 7–22 (mean 14) hours in adults, indicating more rapid elimination in the younger age group and the need for eight hourly administration. In 11 of the 13 children oral FA resulted in successful prophylaxis. Control was achieved with plasma concentrations of FA ranging from 128 μl to 940 μl (mean 473 μg/l). No side effects were reported (mean follow up 18 months).

FA is a safe and effective drug for both short term and long term management of refractory SVT in children.

Doppler echocardiographic study of the changes in intracardiac blood flow and gestational age in the human fetus

J Kenny, T Plappert, P Doubilet, D Saltzman,
M St John Sutton
Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

To assess the changes with gestational age in right ventricular and left ventricular stroke volumes and intracardiac blood flow velocities in the normal human fetus we obtained Doppler echocardiographs in 80 fetuses (gestational age 19–40 weeks). Doppler velocity spectra of aortic, pulmonary, tricuspid, and mitral flow were digitised to obtain peak velocities and flow velocity integrals. Diameters of the aorta and pulmonary artery were measured at valve level from cross sectional echocardiographic images and cross sectional areas were calculated. Stroke volume (ml) was calculated from the product of the flow velocity integral and cross sectional area. Aortic and pulmonary artery diameters increased linearly with gestational age ($r = 0{\cdot}84$, $r = 0{\cdot}85$); the pulmonary artery was consistently bigger than the aorta ($p<0{\cdot}001$). Left ventricular stroke volume and right ventricular stroke volume increased exponentially with gestational age from 0·6 ml at 20 weeks to 5·0 ml at 40 weeks ($r = 0{\cdot}93$) and from 0·5 ml at 20 weeks to 6·9 ml at 40 weeks ($r = 0{\cdot}88$) respectively. In fetuses in which it was possible to record both pulmonary artery and aortic flows, right ventricular stroke volume was greater than left ventricular stroke volume in the ratio of 1·2:1 ($r = 0{\cdot}97$) ($p<0{\cdot}001$). Transmitral and tricuspid flow velocities were greater during atrial systole than during rapid filling, and flow velocity did not vary with gestational age.

This study demonstrates that right and left ventricular stroke volumes increase by over tenfold from 20 to 40 weeks and that right ventricular stroke volume exceeds left ventricular stroke volume by 20%.

Are major cardiac defects invariably recognised in the newborn infant?

K A Hallidie-Smith, P Morais
Royal Postgraduate Medical School, London

Examination of the heart is recognised as being an important component of the examination of the newborn infant. The trend to earlier discharge during the period of potential functional ductus patency, however, could cause difficulties in assessment. We reviewed the records of 200 consecutive admissions of neonates born in the United Kingdom who were found to have major cardiac anomalies leading to urgent surgery or causing death. Sixty four (32%) had been sent home as having normal hearts between the ages of 24 hours and 10 days (mean 3·0 days). They were admitted 1–29 days later and urgently transferred within 24 hours. Twelve infants collapsed at home; most re-presented for multiple reasons of which poor feeding (41) was the most common. On transfer 39 were in severe heart failure and 10 were centrally cyanosed. All 64 had abnormal breathing patterns and abnormal second heart sounds; those in heart failure had a loud gallop. Only four had loud systolic murmurs. The most common missed malformations were coarctation of the aorta (17) and hypoplastic left heart (12). While delayed diagnoses were made in cyanotic infants with total anomalous pulmonary venous drainage (four), pulmonary atresia (four), and single ventricle (five), infants with simple transposition were referred early and directly.

It is concluded that many major cardiac defects are difficult to diagnose in early neonatal life, particularly during ductus patency, and that many such infants may pass as normal. The feeding history is particularly relevant and the absence of murmur does not preclude a potentially fatal cardiac defect. A greater level of awareness of this possibility by both hospital and home medical and nursing staff could lead to earlier diagnosis, which in some instances could enhance the infant's chances of survival.

Balloon angioplasty for coarctation of the aorta in infants and children

J V De Giovanni, J G C Wright, E D Silove
Department of Cardiology, Children's Hospital, Birmingham

Balloon dilatation for arterial stenosis has been performed extensively and with success, but experience in aortic coarctation is limited. We carried out balloon angioplasty for coarctation in 11 patients, six with native coarctation (group 1) and five with recoarctation (group 2). Six had other associated congenital heart defects in addition to coarctation. Four patients in group 1 presented with heart failure, one had hypertension, and in one angioplasty was elective. The five patients with recoarctation had hypertension. The age at the time of angioplasty ranged from 6 days to 15·5 years in group 1 and from 7 months to 4·5 years in group 2. After angioplasty the mean (SD) peak systolic gradient dropped from 42 6 (17·5) to 14·5 (9·2) mm Hg ($p < 0{\cdot}01$), with two patients showing no appreciable reduction in gradient. There were no major complications resulting from the technique although two patients in group 1 died, one after surgery and the other from cerebral insult. The longest follow up since dilatation in group 1 is 17 months. The mean duration from angioplasty in group 2 is 6·4 months (range 2–12 months). Surgical repair after angioplasty was required in two patients in group 1 and in one patient in group 2.

Balloon dilatation for native coarctation is effective and should be considered as an alternative to surgery in high risk cases. Angioplasty is the method of choice for recoarctation.

Exertional gastro-oesophageal reflux: a possible mechanism for symptoms in patients with angina pectoris and normal coronary angiograms

P M Schofield, D H Bennett, N H Brooks, P E Jones, P J Whorwell, C L Bray, C Ward
Regional Cardiac Centre, Wythenshawe Hospital, Manchester

Nineteen men and 21 women (aged 30–65 years) with typical angina pectoris and normal coronary angiograms underwent symptom limited exercise testing (Bruce protocol) during 24 hour oesophageal pH monitoring to determine whether exertional gastro-oesophageal reflux ($pH < 4$) occurred. Sixteen patients had gastro-oeosphageal reflux during exercise (group 1) and 24 did not (group 2). On the treadmill all 16 patients in group 1 experienced a chest pain coincident with reflux, compared with only 10 in group 2 ($p < 0{\cdot}01$). ST segment response was abnormal ($\geqslant 1$ mm depression) during exercise in seven (44%) group 1 patients and nine (38%) from group 2. The number of episodes of chest pain associated with gastro-oesophageal reflux during 24 hour pH monitoring was greater for group 1 patients (2·6 (1 3), mean (SD) than group 2 (0 71 (1·1)), $p < 0{\cdot}01$. There was no difference, however, between groups 1 and 2 in the number of episodes of pain not associated with gastro-oesophageal reflux (0 94 (1·0) and 0·88 (0·9) respectively). Lower oesophageal sphincter pressure, measured during oesophageal manometry, was less in group 1 patients (12 1 (3·8) mm Hg) than in group 2 patients (18 4 (6 9) mm Hg) ($p < 0\ 01$).

In conclusion, exertional gastro-oesophageal reflux may account for the symptoms of some patients with angina pectoris and normal coronary angiograms.

Continuous recording of coronary sinus oxygen saturation during atrial pacing in patients with and without coronary artery disease or with syndrome X

T Crake, P Crean, L M Shapiro, R Canepa-Anson, P A Poole-Wilson
Cardiothoracic Institute and National Heart Hospital, London

In the normal heart coronary blood flow increases in proportion to cardiac work so that sufficient oxygen and substrate are supplied to the myocardium and excess metabolites are removed. Continuous coronary sinus oxygen saturation was recorded during an incremental pacing test in patients undergoing cardiac catheterisation. In 10 patients with no evidence of myocardial ischaemia and normal coronary arteries an increase in heart rate increased oxygen extraction but after 15 seconds the coronary sinus oxygen saturation returned to control values. In 10 patients with coronary artery disease and electrocardiographic changes the increased extraction of oxygen persisted and increased with increasing heart rate. Six patients (four women and two men, 38–58 years) had normal coronary arteries, chest pain, and positive exercise tests (syndrome X). In five of these patients though ST segment depression occurred on atrial pacing the change in coronary sinus oxygen saturation was similar to that in patients without coronary artery disease. In one patient, who also had right bundle branch block, an ischaemic response was observed.

Oxygen extraction in the coronary bed of man can be increased by up to 30% but a persistent increase in oxygen extraction is an indication of ischaemia and occurs in the presence of coronary artery disease. Syndrome X does not describe a homogenous group of patients but in most of them the coronary sinus oxygen saturation response is normal, indicating that reduced oxygen supply is not the cause of their symptoms or the electrocardiographic changes.

Mechanisms of ergometrine induced coronary artery spasm

D Hackett, S Larkin, S Chierchia, G Davies, A Maseri
Royal Postgraduate Medical School, Hammersmith Hospital, London

Intravenously administered ergometrine is the most powerful stimulus known to provoke coronary spasm in patients with variant angina (VA) but the drug has a weak action on isolated human coronary artery rings in vitro. To investigate whether ergometrine acts directly on coronary arteries or via remote neurohumoral reflexes we administered small titrated increments of intracoronary ergometrine up to a maximum cumulative dose of 50 μg to 15 patients. In six patients with VA (group 1) ischaemic ECG ST changes ($>0{\cdot}1$ mV), angina, and localised coronary spasm (local coronary diameter reduction of 66–100 (mean 88·8)%) followed 1–3 minutes after 6–50 (20·7) μg cumulative intracoronary ergometrine. In nine patients with atypical chest pain, normal baseline coronary arteriograms, and no evidence of VA (group 2) there was no ischaemic ST segment change or localised coronary spasm after 6–50 (31·6) μg intracoronary ergometrine. The coronary diameter of proximal vessels of patients in group 2 was reduced by 3–24 (16·5)% and did not differ from the response of non-spastic vessels of comparable size in group 1 (7–39 (16·6)%, $p = 0{\cdot}7$). The differences in ED^{50} in the dose response curves of spastic and non-spastic segments in groups 1 and 2 were not significant. Coronary spasm, ST segment changes, and pain were all immediately reversed after 2 mg intracoronary isosorbide dinitrate and there were no side effects.

Therefore, ergometrine causes spasm by a direct local coronary effect which seems due to a localised arterial hyperreactivity rather than supersensitivity. The intracoronary route may be safer than the intravenous one because negligible drug recirculation may prevent perpetuation of spasm and selective coronary administration can avoid branches with critical stenoses.

End-tidal pco$_2$ on exercise in the diagnosis of non-cardiac chest pain

J B Chambers, P S Kiff, W N Gardner, G Jackson, C Bass
Cardiac Unit, King's College Hospital, London

We have measured end-tidal pco$_2$ during 113 routine treadmill exercise tests for the assessment of chest pain. The conventional exercise test was diagnostic in 15 patients and in 13 (87%) of these the pco$_2$ stayed consistently above 30 mm Hg. Of the remaining 98 patients, 28 (29%) had hypocapnia (HC) during exercise (pco$_2$ < 30 mm Hg) and by the fifth minute of recovery 49 (50%) patients had developed HC. Patients in whom HC developed had significantly more symptoms suggesting hyperventilation (HV) and depression, but not anxiety, than patients with a normal pco$_2$ response. Formal HV provocation testing reproduced pain in 50% patients who had HC during exercise and in 38% with HC during recovery. Despite this, chest pain developed in 44% of the total sample during the test and was not related to changes in pco$_2$. This suggests that factors other than HC may contribute to the reporting of chest pain. Three of five patients with painless ST depression of $\geqslant 1{\cdot}5$ mm had HC. Although HC is a possible mechanism for ST depression, 42 (37%) patients of the total sample developed ST depression of 0·5–3·0 mm that was not related to changes in pco$_2$.

We conclude that monitoring end-tidal pco$_2$ during exercise gave valuable diagnostic information in 43% patients: it confirmed HC in 67% patients with symptoms suggestive of HV and was associated with a 45% incidence of positive HV provocation tests. We therefore suggest that the concurrent measurement of end-tidal pco$_2$ should become routine during treadmill exercise testing especially for assessing atypical chest pain.

Therapeutic implications of silent myocardial ischaemia

P A Crean, T Crake, A A Quyyumi, C Wright, L Mockus, K M Fox
The National Heart Hospital, London

Patients with stable angina pectoris have frequent episodes of silent myocardial ischaemia during ambulatory ST segment monitoring. Whereas current medical treatment is known to reduce the number of anginal attacks, little is known about the best treatment for these silent ischaemic episodes. We performed frequency modulated ambulatory ECG monitoring in 48 patients with chronic stable angina to assess the effect of three β blockers with different properties and nifedipine on the frequency of silent myocardial ischaemia compared with placebo treatment. Thirty nine men and nine women (mean age 57·8 years) completed the study. All patients had a positive exercise test and coronary stenosis of $>70\%$. There were 341 episodes of ST segment depression during 1835 hours of monitoring on no treatment, of which 57 (17%) were symptomatic and 282 (83%) were silent. During antianginal treatment 559 episodes of ST segment depression were observed, of which 462 (82%) were symptomatic and 97 (18%) were silent in 3186 hours of monitoring. Atenolol, labetolol, and nifedipine reduced the total number of episodes of ST segment depression (symptomatic and pain free) compared with placebo treatment by 33%, 55%, and 23% respectively ($p < 0.05$); no significant change was seen during pindolol therapy. The percentage of total episodes that were silent remained constant throughout the placebo and all treatment periods.

Thus antianginal agents that reduce the number of episodes of angina may be expected to reduce the number of silent episodes of ST segment depression by a similar proportion.

Psychological stress as a dynamic factor producing myocardial ischaemia in coronary artery disease

Leisa J Freeman, P G F Nixon, P Sallabank
Charing Cross Hospital, London

Thirty patients with symptomatic coronary artery disease (CAD) were studied on two separate occasions to investigate sources of variability in episodes of ischaemia as documented by ambulatory ST monitoring. The first was six days after outpatient coronary arteriography when the outcome was not yet known and the second about two months later. Medication was tapered off for 72 hours before monitoring. Patients kept detailed diaries to record their activities and episodes of chest pain. We also asked them to document any somatic feelings of anxiety, tension, or emotional upset. Urine was collected during the first 24 hours of each monitoring period for the measurement of cortisol, noradrenaline, and adrenaline. 2711 hours were analysed. During this time there were 515 episodes of ST segment depression, of which 174 (33·8%) were associated with pain and 341 (66·2%) were not. There were no significant differences between periods of monitoring as regards subjective reports of angina or daily activities as assessed from the diaries. There were significantly more episodes of silent ischaemia on the first occasion than the second ($p < 0.007$) and this group of patients reported more episodes of emotional upset ($p < 0.04$). Cortisol excretion was significantly higher on the first occasion than the second ($p < 0.03$). A higher noradrenaline excretion on the first occasion was associated with significantly more episodes of silent ischaemia ($p < 0.05$) and longer ischaemic time ($p < 0.01$). During the first period of monitoring there was a correlation between increasing noradrenaline excretion and total ischaemic time ($r = 0.4$; $p < 0.04$). Psychological stress on the first occasion may be an important variable factor producing ischaemia.

Percutaneous aortic valvuloplasty for aortic stenosis

G Jackson, M Monaghan, S Thomas, D Jewitt
Cardiac Department, King's College Hospital, London

Symptomatic aortic stenosis may reduce the quality of life for older people who are poor candidates for surgical treatment. We attempted percutaneous valvuloplasty from the femoral artery in fifteen patients. All were severely disabled by heart failure (New York Heart Association IV) or angina. Olbert balloon catheters were advanced to the aortic valve. They were stabilised by a guidewire in the left ventricle. Balloons measuring 6, 8, 10, 12, and 14 mm were used. Initial gradients across the valve varied from 80 to 140 mm Hg. The balloon was inflated under echocardiographic guidance to the cusp position. In 14 patients a satisfactory symptomatic and haemodynamic result was achieved. Gradients fell by up to 50% and Doppler studies at 3 month follow up showed that this fall was maintained. Patients immediately noticed a reduction in breathlessness, especially at night. One patient died four hours after the procedure, which was done as an emergency procedure when the patient was moribund (gradient 140 mm Hg). One patient had a drop in systemic pressure after inflation of a 14 mm balloon but recovered quickly. No significant increase in aortic incompetence was noted.

Percutaneous valvuloplasty for inoperable severe aortic stenosis is highly effective in relieving symptoms and provides a new treatment for inoperable elderly patients.

Balloon aortic valvuloplasty for severe calcific aortic stenosis: effective but not without hazard

I R Starkey, D C Cumberland, G D G Oakley
Cardiology Department, Northern General Hospital, Sheffield

Four patients aged 56–79 years with severe calcific aortic stenosis were treated with percutaneous balloon aortic valvuloplasty after they had been considered to be unsuitable for surgery for various reasons.

Three different designs of balloon catheter were used. One patient, who was in severe intractable pulmonary oedema, died during the procedure; necropsy showed that the valve had been satisfactorily split. The other three patients' symptoms improved after the procedure, which also led to an improvement in measured haemodynamic variables, notably the transvalvar gradient (which fell from 70–124 mm Hg to 30–50 mm Hg) and the calculated valve area. In one patient the systolic aortic pressure fell to 70 mm Hg during balloon inflation without symptoms. In another the systolic aortic pressure fell to the same level as the systolic pulmonary arterial pressure within 10 seconds of balloon inflation; this was associated with severe dizziness. This was not prevented by use of the Trefoil balloon whose geometry it is claimed should help to avoid this hazard. One patient developed syncope during each inflation; in this case deflation of the balloon through the 8F catheter was prolonged and systolic aortic pressure became temporarily unrecordable. One patient suffered a small stroke 16 days after the procedure.

Although balloon aortic valvuloplasty should be considered as a possible form of treatment for patients with calcific aortic stenosis who are thought to be too elderly or unfit for conventional surgical treatment, careful documentation is required to determine the true incidence of side effects and complications.

How does aortic balloon valvoplasty work?

D J M Reynolds, D L Stone, F C Wells, M C Petch
Regional Cardiac Unit, Papworth Hospital,
Papworth Everard, Cambridgeshire

Four patients (2 male, 2 female, age 53–68, mean 61) with calcific aortic stenosis underwent balloon valvoplasty intra-operatively under direct vision immediately before valve replacement. A 9F 12 mm diameter balloon was placed across the valve and inflations were performed for 10–15 seconds at eight atmospheres, eight atmospheres, and 12 atmospheres. Video recordings and photographs were taken before and after each inflation. After excision the valves were *x* rayed and examined histologically. In each case satisfactory dilatation was obtained. The valve leaflets did not split nor was there any evidence of fracturing of calcium which might have led to embolisation. In two instances complete obstruction of the stenosed valve orifice occurred during dilatation. Dilatation was achieved by stretching of the remaining non-calcified portions of the valve.

Aortic balloon valvoplasty is an effective means of valve dilatation and fears of embolisation and valve tearing were not supported. Dilatation time should be kept to a minimum to avoid prolonged obstruction to cardiac output.

Intermediate term results of percutaneous balloon pulmonary valvoplasty

J A Ettedgui, E J Baker, O D H Jones, J Reidy,
M J Tynan
Guy's Hospital, London

Twenty five patients (age range 6 days–17 years) with valvar pulmonary stenosis treated with percutaneous balloon pulmonary valvoplasty (PBPV) have been assessed by cardiac catheterisation a mean of 10·3 months (range 2 weeks–37 months) after PBPV. At this stage the right ventricular (RV) pressure (56 (17) *vs* 80 (18) mm Hg, transvalvar gradient (32 (16) *vs* 59 (19) mm Hg, and RV:systemic pressure ratio (0·54 (0·26) *vs* 0·79 (0·21)) for the group as a whole were significantly lower than before PBPV ($p < 0·001$ for each variable). Seven patients, in five of whom the immediate result was considered to be good, had unsatisfactory results at follow up. Three have had repeat PBPV; two of them had good results on subsequent restudy; the third has not yet been restudied. Initial failure in these three cases has been attributed to the use of too small a valvoplasty balloon, the diameter being equal to or less than that of the pulmonary valve ring. Four patients have been referred for surgery: three of these had severely dysplastic valves and one had additional fixed subvalvar pulmonary stenosis. A further three patients had moderately raised RV pressures with a RV:systemic pressure ratio just over 0·5 at follow up, but less than before PBPV. Excluding the patients who were subsequently referred for surgery, PBPV had intermediate term success in 71%. This increased to 88% when a valvoplasty balloon with a diameter up to 20% larger than that of the pulmonary valve ring was used.

We conclude that PBPV is effective for the treatment of valvar pulmonary stenosis. The main causes of failure are (*a*) severely dysplastic valves, (*b*) fixed subvalvar pulmonary stenosis, and (*c*) valvoplasty balloons that are not large enough. Careful selection of patients and valvoplasty balloons will give the best results.

Long term follow up in biopsy proven myocarditis: progression to dilated cardiomyopathy

P J Quigley, P J Richardson, B T Meany,
E G J Olsen, M Monaghan, G Jackson, D E Jewitt
Cardiac Department, King's College Hospital,
London, and National Heart Hospital, London

Acute myocarditis has been implicated in the aetiology of dilated cardiomyopathy. To investigate the natural history of acute myocarditis and progression to dilated cardiomyopathy 23 patients with biopsy proven acute myocarditis were serially followed at 2, 6, and 12–24 monthly intervals by clinical, echocardiographic, haemodynamic, and histological evaluation. Assessment of left ventricular function by radionuclide ventriculography was performed at late (4–5 years) follow up and patients with impaired left ventricular function were restudied by catheter biopsy. The ejection fraction (EF) was severely impaired in 81% of patients at diagnosis (31 (4%), mean (SEM)). After six months two groups were evident: in group 1 left ventricular function was normal (EF (62 (2)%, n = 9) and in group 2 it was impaired (EF 29 (5)%, n = 8), $p < 0{\cdot}001$). At late (4–5 years) follow up seven of the nine group 1 patients, all of whom remained clinically normal, had abnormal EF response to exercise (rest 68 (3)%; exercise 62 (3)%). Seven of the eight group 2 patients had persistent impairment of left ventricular function. Altogether, characteristic features of dilated cardiomyopathy developed in 12 (52%) patients; four of them died. In nine histological findings were consistent with the clinical diagnosis and three were diagnosed by non-invasive assessment alone.

Assessment of left ventricular function at six months in patients after acute myocarditis predicts outcome. Late follow up has shown progression to dilated cardiomyopathy in 50% and most have persistent impairment of cardiac reserve.

Viral myocarditis in children

J Ettedgui, E J Baker, S E M Clarke, O D H Jones,
M N Maisey, S Qureshi, M J Tynan
Guy's Hospital, London

Ten children aged 4–47 months (mean 22 months) with the clinical diagnosis of viral myocarditis had serial nuclear angiographic assessment of left ventricular (LV) ejection fraction (EF), right ventricular (RV) EF, and phase analysis (PA) for detection of dyskinesis. All had RV endomyocardial biopsy (EMB) because of persisting symptoms. Initial EMBs were performed 1–10 months (mean 4 months) after the onset of the illness. At presentation LVEF was 21 (6)%, RVEF 54 (17)%, and PA showed dyskinesis in nine. EMB showed chronic active inflammatory changes in three patients, inflammation with fibrosis in five, and no abnormality in two. All three patients with chronic active inflammatory changes alone were treated with prednisolone and azathioprine for 6–12 months. Two showed complete clinical and histological recovery, their LVEF returned to normal and the dyskinesis disappeared. Interstitial fibrosis was seen in the one who died, and there was a persistent low LVEF with progressive deterioration of RVEF. Of the five with inflammation and fibrosis, one was treated as above for one month without improvement; he subsequently died. One treated with prednisolone alone for six months showed no improvement. One of the remaining three untreated patients died. In none of the patients in this group has the LVEF returned to normal or the dyskinesis disappeared. Of the two with normal histological results, one died and one has persisting low LVEF, RVEF, and dyskinesis.

These results show that the prognosis of children with symptomatic viral myocarditis is poor. Cardiac performance rarely returns to normal and in this series 40% died. We suggest that in these patients EMB should be performed early. In those with chronic active inflammatory changes, immunosuppression controlled by serial EMB may prove beneficial. This approach requires further investigation.

The acute effects of ethanol on myocardial metabolism in patients with alcohol induced heart muscle disease

B T Meany, P J Richardson, Lynne Atkinson,
G Bergman, S Kerkez, D E Jewitt
Cardiac Department, King's College Hospital,
London

The acute effects of ethanol on myocardial metabolism were investigated in six patients with confirmed alcoholic heart muscle disease. Coronary sinus and femoral artery concentrations of substrate were determined 15, 30, 45, and 60 min after an oral dose of 6 oz alcohol. Arterial concentrations of ethanol rose to 0 78 (0·05) mg/ml (mean (SEM) at 30 min and declined slightly to 0·51 (0·05) mg/ml at 60 min. Arterial and venous concentrations of lactate rose from 1·04 (0·13) to 2·09 (0·19) mmol/l ($p < 0{\cdot}001$) and from 0·77 (0·15) to 1·5 (0·26) mmol/l ($p < 0$ 005) respectively, reflecting lactate release from the liver.

Arterial and venous concentrations of pyruvate fell from 62·1(10·5) to 40·8(6·4) μmol/l ($p < 0{\cdot}05$) and from 38·5(6·9) to 35·3(6·0) μmol/l respectively. Thus the arteriovenous difference and extraction ratio for lactate were unchanged, but for pyruvate they fell from 23·5 (5·3) to 5·3 (3·8) μmol/l ($p < 0{\cdot}005$) and from 35·9(6·9) to 11·3 (13·3)% ($p < 0{\cdot}05$) respectively. The coronary sinus lactate:pyruvate ratio rose from 0·022(0·003) to 0·051(0·009) ($p < 0{\cdot}02$), reflecting an increase in myocardial redox potential. Glucose and oxygen concentrations were unchanged. Although arterial concentrations of noradrenaline were unchanged, coronary sinus concentrations rose from 737(146) to 1001(225) pg/ml ($p < 0{\cdot}02$).

These results suggest that the effects of ethanol on myocardial metabolism in patients with alcoholic heart muscle disease may be mediated by ethanol induced changes in hepatic metabolism, resulting in increased myocardial redox potential.

Evidence of left ventricular relaxation abnormality in patients with acromegaly

E A Rodrigues, M P Caruana, A Lahiri,
J D N Nabarro, H S Jacobs, E B Raftery
Northwick Park Hospital and the Middlesex
Hospital, London

It has long been thought that there is a specific cardiomyopathy in acromegaly. To investigate this possibility 27 patients with a history of acromegaly were studied by treadmill exercise tests (GXT) and radionuclide angiography. Of these, eight (30%) showed evidence of ischaemic heart disease (positive GXT or wall motion abnormality or both) or hypertension and were excluded from further analysis. In the remaining 19 patients the results of radionuclide angiography were compared with those obtained from 30 normal volunteers. The mean (SD) normal resting values were: ejection fraction (EF) 62(6)%, ejection rate (ER) 1·9(0·4) EDV/s, ejection time (ET) 340(40) ms, peak filling rate (PFR) 3·1(0·4) EDV/s, early filling rate (EFR) 1·5(0·4) EDV/s, time to peak filling rate (TPFR) 168(50) ms, filling fraction (FF) 0·5(0·02). In the patients the values were: EF 58(10)% (p = NS), ER 2·0(0·6) EDV/s (p=NS), ET 330 (62) ms (p = NS), PFR 2·2 (0·65) EDV/s ($p < 0{\cdot}01$), EFR 1·1 (0·5) EDV/s ($p < 0{\cdot}01$), TPFR 194 (70) ms (p = NS), FF 0·36 (0·2) ($p < 0{\cdot}01$). During exercise there was no difference in EF between normal subjects and patients but exercise FF was lower in the patients ($p < 0{\cdot}05$).

This study demonstrates that left ventricular systolic function is normal in acromegaly but left ventricular diastolic function is significantly impaired even in patients with no overt cardiac symptoms. This reduced left ventricular compliance may be related to the interstitial fibrosis and mononuclear infiltrate previously demonstrated in patients with acromegaly; hence left ventricular diastolic indices may be an early and sensitive indicator of cardiac involvement in acromegaly.

Analysis of left ventricular segmental wall motion versus coronary patency after thrombolytic treatment

S G Richardson, Patricia Morton, J G Murtagh,
M E Scott, D B O'Keeffe
Cardiac Unit, Belfast City Hospital, Belfast

Two hundred and five patients with severe cardiac infarction were treated with 1·5 megaunits intravenous streptokinase at a mean time of 173 min (5–495) after onset of symptoms. All patients had coronary arteriography and left ventriculography (30° right anterior oblique view) 4–10 days after treatment. The infarct related artery was patent at study in 159(77·6%). There was no significant difference in age, sex, site of infarct, or duration of symptoms between those patients with open and those with closed infarct related arteries. Left ventriculograms were analysed to measure ejection fraction (LVEF) and divided into 48 equal radial segments; radial systolic shortening <26% was defined as hypokinesis and <11% as akinesis. Indices representing hypokinesis and akinesis were derived. LVEF in the open artery group (46·5(2·1) (mean (2SE)) was slighly better than in the closed artery group (42·6(3·0)) ($p < 0{\cdot}1$). Hypokinesis was significantly greater in the closed artery group (462·8(54·0)) than in the open artery group (388·0(31·6)) ($p < 0{\cdot}05$). Akinesis was markedly less in the open artery group (101·2(16·1)) than in the closed artery group (161·1(38·4)) ($p < 0{\cdot}01$). We were unable to identify any important difference in hyperkinesis between the two groups.

Infarction leads to segmental myocardial dysfunction, and indices of global left ventricular function give only a crude measure of this. Hypokinesis may reflect partial thickness infarction, marking the area of myocardium subtended by the affected coronary artery. This feature was only slightly different in the two groups (open and closed arteries) examined. Akinesis of the left ventricular wall represents full thickness necrosis and this was much more extensive in the patients with persistent coronary occlusion. Successful thrombolysis, where the infarct related artery remained open, was associated with substantially less severe regional left ventricular wall abnormality, particularly less extensive akinesis, suggesting significant myocardial salvage.

Do infarct related coronary stenoses become remodelled after successful thrombolysis?

D Hackett, Phoebe Gavrielides, S Larkin,
S Chierchia, G Davies, A Maseri
Royal Postgraduate Medical School, Hammersmith Hospital, London

Severe coronary stenoses usually persist after thrombolysis in acute myocardial infarction (AMI) but whether there are any subsequent early changes in their severity is unknown. Twenty patients with AMI who had successful thrombolysis were studied by coronary arteriography immediately after thrombolysis (20 cases), at 24 hours (17 cases), and at three months (13 cases). Coronary arteriography was also repeated after 2 mg of intracoronary isosorbide dinitrate. Quantitative coronary arteriograms in standardised end diastolic views were obtained from a computerised automatic edge detection analysis system (CAAS; Pie Data Medical) The minimal luminal diameter of infarct related coronary stenoses increased from 1·13(0·3) mm (mean (SD)) immediately after thrombolysis to 1·34(0·5) mm at 24 hours ($p=0·005$ paired *t* test) but no further change had occurred by three months (to 1·38(0·3) mm, $p=0·2$) whereas the diameter of adjacent normal prestenotic segments did not change with time. Intracoronary isosorbide dinitrate caused significant dilatation of the stenosis to 1·47(0·6) mm ($p=0·02$) immediately after thrombolysis and to 1·68(0·6) mm ($p=0·003$) at 24 hours. The difference between the nitrate dilated stenosis immediately after thrombolysis and at 24 hours was less significant ($p=0·08$).

Residual coronary stenoses after successful thrombolysis for AMI are usually but not always severe and they improve within 24 hours but do not change further at three months. The differences in severity of infarct related coronary stenoses within 24 hours of AMI are less after smooth muscle relaxation, which suggests that both a reduction in coronary vasoconstrictor tone and stenosis remodelling are responsible for the changes.

Thrombolytic treatment in acute myocardial infarction in the elderly

F A Johnston, F G Dunn, K J Hogg, R S Hornung,
W S Hillis
Departments of Geriatric Medicine, Materia Medica, and Cardiac Department, Stobhill General Hospital, Glasgow

Thrombolytic treatment has an increasing role in the treatment of acute myocardial infarction to promote coronary artery reperfusion, to decrease infarct size, and preserve left ventricular function. In general, the elderly have been excluded from previous studies. Fifty seven patients (35 men, 22 women, aged 65–80 years, mean 70 years) with cardiac pain lasting >30 min and confirmatory ECG evidence of acute myocardial infarction received thrombolytic treatment within eight hours of onset of symptoms with either streptokinase or acylated plasminogen streptokinase complex (APSAC) by the intracoronary or intravenous routes. Coronary artery reperfusion was confirmed by early coronary arteriography. 89% had either double or triple vessel disease. The overall reperfusion rate was 75% (similar to that in young age groups) with similar success for each major vessel: left anterior descending 75%, right coronary artery 81%, circumflex 80%. Clinical events suggesting early reocclusion occurred in 23%. Early coronary arteriography was accompanied by local bleeding, which required transfusion in two patients, and a cerebrovascular accident in one patient Minor bleeding occurred in six other patients. In those in whom reperfusion was obtained the mortality at one month was 6·6% and in those in whom it was not or who had early reocclusion it was 38%; at one year it was 10% and 46% respectively.

Thrombolytic treatment is effective and safe in promoting reperfusion in the elderly and appears to have beneficial effects on early mortality. Application of non-invasive markers of reperfusion seems to be appropriate in this age group.

Thrombolysis in Coronary Occlusion (TICO) trial: how many patients with myocardial infarction might benefit from early (<2·5 h) thrombolysis?

G I C Nelson, M O'Rourke, J Raftos, R Norris
Australia New Zealand TICO Working Group, Sydney, Australia

The narrow time window for thrombolysis to be maximally effective in myocardial infarction (MI) has been thought to be the major problem with this treatment. We reviewed the reasons for exclusion of patients from randomisation during the first twelve weeks of the Thrombolysis in Coronary Occlusion (TICO) study in which the effect of treatment with recombinant tissue type plasminogen activator (rt-

PA) on left ventricular function was compared with that of placebo in a double blind trial. This trial is being conducted in central Sydney (population about 720 000) in patients aged 72 years presenting within 2·5 h of onset of symptoms of first MI unrelieved by nitrates and without contraindications to thrombolytic treatment. Of 132 patients with confirmed MI, 31 (23%) fulfilled all the eligibility criteria and 27 (20%) were entered. Forty (30%) of 132 were excluded because of delayed presentation alone. Other primary exclusion criteria were age (19 (14%)), previous MI (17 (13%)), non-diagnostic electrocardiograms (22 (17%)), and history of gastrointestinal bleeding or dyspepsia (2 (2%)). An additional patient who had had glyceryl trinitrate for pain relief was also excluded. Most of these criteria would not preclude thrombolysis in a non-trial setting even in a district hospital.

We estimate that in an informed community with alert emergency room and ambulance paramedical staff, early (< 2·5 h) intravenous thrombolytic treatment might be applicable to at least 45% of patients with myocardial infarction, assuming that the average time to presentation could be reduced by only one hour.

Is Doppler of value in the diagnosis or assessment of coarctation of the aorta?

L A Simpson, A B Houston, W B Doig,
M P G Jamieson, J C S Pollock, E N Coleman
Royal Hospital for Sick Children, Glasgow

Doppler studies have been performed on a consecutive series of 45 infants and children (2 days–16 years, 1·0–58 kg) with coarctation of the aorta or arch interruption undergoing surgery with or without previous catheterisation. While an increased blood velocity apparently from the arch was found in 19 of the 20 infants with coarctation this was also demonstrated in two of the three with arch interruption. In one with coarctation inflation of a balloon in the ductus abolished the signal, suggesting that ductal flow had been obtained. Thus an increased velocity in the arch cannot always be detected in infants with coarctation and when it is found it may be caused by ductal flow and thus does not distinguish coarctation from interruption. In older patients an increased velocity was found in only 19 of the 22. In the 22 in whom pressures were measured proximal and distal to the coarctation at catheterisation there was a poor correlation (r = 0·41) between Doppler and measured gradients that was not due to the difference between peak to peak and instantaneous maximum pressure differences. Since the pressure drop does not accurately reflect the severity of the obstruction there is little practical value in attempting to measure this with Doppler in the child presenting with coarctation.

Our observations seem to refute previous suggestions that Doppler allows accurate diagnosis of coarctation and measurement of pressure drop across the obstruction. We conclude that coarctation of the aorta is one congenital cardiac lesion in which Doppler has little to add to clinical and echocardiographic assessment.

Flail or torn cusps of tissue valve prostheses diagnosed by Doppler ultrasound

J B Chambers, M J Monaghan, G Jackson,
D E Jewitt
Cardiac Unit, King's College Hospital, London

We have noted a characteristic abnormality of the Doppler signal associated with a tear in one cusp of failing non-stenotic tissue valves. Five patients, four with mitral protheses (2 Hancock, 1 Carpentier-Edwards, and 1 CT1 bovine pericardial) and one with a homograft aortic prosthesis were studied a mean of eight years after operation. All had loud high pitched regurgitant murmurs. In four cases increased motion of one cusp was seen on the cross sectional echocardiogram. The Doppler audiosignal in all cases was harsh and musical. The regurgitant flow pattern was bidirectional and striated. There were 4–6 striations in the mitral and 18 in the aortic regurgitant jets per 100 cm/s length of signal. The mean peak inflow velocity for the four mitral prostheses was 2·0 m/s and the mean pressure half time was 60 ms. Pulsed Doppler localised the jet to the valve in all cases. Angiography was performed in four cases and failed to localise the jet in one. At operation two cases had partial disintegration of one cusp and in one case each there was one cusp torn for about 0·5 cm from its commissure, a perforation of one cusp, and one cusp torn from both commissures. There was no evidence of dehiscence of the sewing rings and in every case the other cusps were mobile and intact.

We conclude that striation of the Doppler signal from the regurgitant jet in a failing tissue prosthesis is likely to be a useful sign of a torn or flail cusp.

Magnetic resonance velocity mapping: clinical application of a new technique

S R Underwood, D N Firmin, R H Klipstein,
R S O Rees, D B Longmore
Magnetic Resonance Unit, National Heart and Chest Hospitals, London

Magnetic resonance velocity mapping is a new technique providing a display of velocity within the cardiovascular system at any point of the cycle. Velocity is encoded either in the image plane or perpendicularly to it, and the temporal resolution is typically 50 ms. Colour coding of the display and superimposition on a conventional image allows a combined assessment of both anatomy and flow. The technique has not previously been used clinically and we report the findings in six patients, illustrating some of the areas in which it may be of value. In a patient with coronary artery bypass grafts high velocities were seen in one graft with good run off (326 m/s peak) and low velocities (74 mm/s peak) in a graft with poor run off. Velocity was high in an iliac vein partially occluded by thrombosis (213 mm/s peak) and low distal to an aortic coarctation (103 mm/s peak), confirming the functional importance of the lesions. Flow was seen through an atrial and a ventricular septal defect and through a Gerbodie defect. Turbulent flow distal to the ventricular defects led to some loss of quantitative information, but it was still possible to estimate the relative sizes of the shunts. In a patient with left isomerism it was difficult to distinguish the descending aorta from the azygos vein by conventional imaging, but velocity mapping provided the distinction and clarified the anatomy.

Magnetic resonance velocity mapping promises to provide useful information in a wide range of disorders of the cardiovascular system and may avoid the need for invasive investigation in some cases.

The practical application of Doppler to patients with a ventricular septal defect

A B Houston, I A Simpson, W B Doig,
M P G Jamieson, J C S Pollock, E N Coleman
Royal Hospital for Sick Children, Glasgow

The recording of flow and measurement of the pressure differences between the ventricles has two important potential applications in patients with a ventricular septal defect (VSD). These are the determination of the presence of pulmonary hypertension and the need for surgical closure in the first few years of life, or the confirmation of its presence and the need for prophylaxis against infective endocarditis in older patients. Doppler ultrasound has been used in a consecutive series of 69 patients with VSD undergoing cardiac catheterisation. The overall correlation between Doppler and measured gradient was 0·92, with little difference between peak to peak and instantaneous maximum gradient in the 22 in whom simultaneous measurement of both ventricular pressures was made. A Doppler value of <30 mm Hg was always associated with significant right ventricular and pulmonary hypertension (22 patients) while one between 30 and 50 mm Hg (9 patients) was sometimes associated with significant pulmonary hypertension. A value >50 mm Hg was associated with relatively low right sided pressures (39 patients); the VSD flow jet was recorded in all these patients including those with small defects not apparent on echocardiography.

Since accurate estimate of left ventricular systolic pressure from arm blood pressure is often difficult and may be inaccurate it is suggested that simple measurement of ventricular pressure difference allows selection of those with possible pulmonary hypertension for further investigation. In older symptom free patients with a murmur and normal echocardiographic results, Doppler may be the most sensitive non-invasive means for determining the presence of a small VSD; further studies are required to ascertain whether it is better than clinical examination.

Why pace the elderly?

C E Handler, P M Holt
Guy's Hospital, London

Over the past five years 275 patients (151 women and 124 men) aged between 85 and 105 (mean 89, with 27 patients aged over 100) years have received permanent endocardial pacemakers. At presentation the main symptoms were syncope (59%), dizzy spells (20%), and heart failure (9%). The ECG showed complete heart block (58%), tachycardia-bradycardia syndrome (14%), second degree heart block (11%), atrial fibrillation (5%), and bifascicular block with prolonged PR interval (0·4%). Most patients were thought to have conduction tissue fibrosis; only 7% had an ischaemic aetiology. Over 98% of the patients were paced in VVI mode. Programmable generators were implanted in 58 patients and voltage could often be programmed to a lower output one month later. Most patients returned to full independence and did not require subsequent lengthy hospital admission. Percentage cumulative survival rates from the first to seventh years were: 84%, 78%, 65%, 57%, 40%, 28%, 28%. Post-implant complications occurred in 34 patients. These were generator change (14), lead reposition (8), lead change (2), lead repair (1), and lead and generator change (9).

These data emphasise the clinical and cost effectiveness of pacing in this age group. Implanting programmable generators and reprogramming to lower voltage outputs may prolong battery life, which is important in elderly patients.

The effect on pacing on exercise performance

M Papouchado, D W Pitcher
Department of Cardiology, Bristol Royal Infirmary, Bristol, Avon

The effect of ventricular pacing on exercise performance was investigated in 18 patients (13 men, aged 53–90 years) with exertional dyspnoea and chronic complete or 2:1 heart block without syncope. Eight patients (6 men, aged 61–80 years) requiring generator replacement served as controls. No patient had overt cardiac failure, significant valvular heart disease, recent myocardial infarction, or surgically induced heart block. A six minute walking test was used to assess exercise performance before, 48 hours after (early), and 1–12 months after (late) pacing (70/min, VVI mode). No training effect was seen in 10 patients who had two walking tests before pacing or in the controls. Pacing increased the mean distance walked from 318·6 (99·9) m to 399·6 (86 4) m ($p < 0{\cdot}001$) after 48 hours to 423 9 (89·1) m ($p < 0{\cdot}05$) for the late walk. Patients reported a reduction in breathlessness after 48 hours which was maintained at follow up. Thirteen patients had repeat walking tests 13 to 30 months after pacing; all remain less breathless, and the improvement in exercise capacity has been maintained in eight of them; walking distance was limited in the other five by arthritis. In the control group generator replacement had no effect on exercise performance (426·6 (83·7) m to 429 (72·9) m at 48 hours, to 432 (67 5) m for the late walk).

We conclude that ventricular pacing improves exercise capacity and reduces symptoms in patients with chronic heart block and breathlessness without overt cardiac failure; this improvement is apparent within 48 hours of pacing and is maintained for up to 30 months.

The comparative safety and success of the endocardial ablation technique applied to His bundles, accessory pathways, and ventricular tachycardia

P Holt, E Boyd
Departments of Clinical Physics and Bioengineering and Cardiology, Guy's Hospital, London

The use of the high energy ablation technique has rapidly expanded into all forms of management of atrial arrhythmias. The generation of large pressure waves renders its use in certain sites potentially hazardous. We report our experience of His bundle (HB), accessory pathway (AP), and ventricular tachycardia (VT) ablation. Forty three patients (24 male, 19 female) aged 22–71 years were referred for His bundle ablation in three years; 37 had atrial fibrillation (AF), three had dual AV nodal pathways (DAVN), and three had concealed AP. Ablation was performed by applying unipolar cathodal shock via one of three different electrodes. Energies ranged from 5 to 250 J (maximum 3 shocks/procedure). Thirty patients required one and 10 required two procedures; only three required three attempts. Persistent complete heart block was produced in 40 (93%) and a further two are symptom free; overall success is 97·6% with no complications. Six patients with APs have been treated; these are three men and three women (aged 36–52 years) three with right and three with left sided AP. Ablation was performed from the right atrium using 20–60 J in the latter group. Conduction was abolished in two and decreased in one with right AP; one patient developed a pericardial effusion. Conduction was decreased but not abolished in only one patient with left sided AP. There were no complications.

Ablation for VT has been attempted in two patients with right ventricular foci without complication. Ablation of VT was successful in one (Helifix electrode with 1 × 50 J shock). Thus ablation of the His bundle is an easy and safe procedure. Ablation of AP and VT foci is possible but it requires careful patient selection and is less successful because only low energies can safely be used.

Termination of ventricular tachycardia by a long duration, low energy, constant current pulse

H M McAlpine, J Christie, D Cunningham, A P Rae, J A Kennedy
Western Infirmary, Glasgow

Successful termination of atrial flutter by a long duration, low energy constant current pulse (Atrioversion) has been reported. This technique has now been applied to both spontaneous and induced sustained ventricular tachycardia (VT) by use of a bipolar endocardial catheter in the right ventricle. Single pulses of fixed duration (longer than the VT cycle length) were delivered in late diastole with progressively increasing energy levels until termination or modification of the tachycardia occurred. Sinus rhythm was regained in seven out of 10 episodes of ventricular tachycardia in five consecutive patients studied to date. The cycle length of the successfully terminated tachycardia was 396 (48) ms (mean (SD)), and the duration of the final pulses delivered was 431 (67) ms with an amplitude 8·6 (4 4) mA. This current corresponds to a delivered energy in the order of 10 mJ. In one unsuccessful attempt the tachycardia was accelerated from a cycle length of 320 ms to 225 ms, but no episode of ventricular fibrillation has been encountered.

Termination of ventricular tachycardia by long pulses is painless and requires only low energy levels. This may have implications for an implantable system.

Acidosis in heart muscle after acute coronary occlusion in man: studies during angioplasty

T Crake, P Crean, L M Shapiro, A F Rickards,
P A Poole-Wilson
The Cardiothoracic Institute, London

The time of onset of acidosis and its relation to the early decline of contractility in ischaemic myocardium is disputed. Coronary sinus pH was recorded continuously in seven patients (4 men and 3 women, aged 43–64) undergoing angioplasty to the left anterior descending coronary artery (LAD). A catheter tip pH sensitive electrode with a response time of less than 300 ms and an ouput greater than 55 mV/pH unit was placed high in the coronary sinus. Coronary sinus pH was recorded continuously during a total of 22 balloon occlusions of the LAD lasting between 6 and 45 s. There was no change in coronary sinus blood pH during occlusion of the LAD but on deflation of the balloon a transient (less than 60 s) fall of pH (washout of hydrogen ions) was observed after a delay of approximately 4 s. In individual patients the peak fall of pH was related to the duration of occlusion of the LAD. The range of fall of pH after occlusions of between 20 and 30 s was wide (0·01 to 0·10 pH units). The largest fall was 0·12 pH units after an occlusion of 45 s. A rise of pH (alkalosis) was never seen. Coronary sinus pH did not change after occlusions of the LAD lasting for less than 12 s ($n = 4$).

In man acidosis occurs in the myocardium after short periods of ischaemia. The acidosis arises from metabolic changes within the myocyte. A substantial fall of pH occurs at the same time as the previously reported loss of potassium and concurrent with the earliest detectable changes of contractile function.

A comparison of intravenous adenosine and atrial pacing in the assessment of coronary perfusion reserve

H Singh, W J Penny, A H Watt, P A Routledge,
A H Henderson
Departments of Cardiology and Pharmacology and
Therapeutics, University of Wales College of
Medicine, Cardiff

We have shown previously that exogenous adenosine is a potent coronary vasodilator. In this study we compared rapid atrial pacing and the responses to bolus injections of adenosine as tests of coronary perfusion reserve. We studied nine patients (41–65 yr, 2 men) with chest pain who had been shown at ateriography to have normal coronary arteries. Great cardiac vein flow (by thermodilution), left ventricular (LV) end diastolic pressure (EDP), and indices of LV contractility (peak dP/dt and dP/dt/P) were measured before and for 60 s after intravenous adenosine (3·5 and 6 mg). Heart rate changes were avoided by right ventricular pacing at 100 beats/min. Great cardiac vein flow (in the last 60 s of each pacing period) was measured in the same patients during an atrial pacing test (beginning at 100 beats/min and increasing by 10 beats/min every three minutes to 150 beats/min). All data are given as mean (SD) and are compared by the paired *t* test. Adenosine 3·5 mg and 6 mg increased great cardiac vein flow by 114 (74)% from 89 (22) ml/min and by 126 (87)% from 93 (23) ml/min respectively ($p < 0{\cdot}001$ in each case). LVEDP, dP/dt, and dP/dt/P did not change. Atrial pacing at 150 beats/min increased great cardiac vein flow by 40 (45)% from 81 (24) ml/min at 100 beats/min ($p < 0{\cdot}05$).

Adenosine increased coronary blood flow three times more than the atrial pacing test did ($p < 0{\cdot}05$), and thus provides a better estimate of coronary perfusion reserve.

Intraoperative recording of the left ventricular myocardial action potential to demonstrate relief of ischaemia

T Treasure, P Taggart, P Sutton, B O'Brien
The Middlesex Hospital, London

The advantages of internal mammary artery (IMA) grafts include excellent long term (10 year) patency and also the potential for growth, resulting in longer duration of symptomatic relief and improved survival. Doubt remains about the adequacy of IMA flow to achieve the immediate revascularisation required when critical lesions are operated upon in patients with unstable angina. We have developed a hand held, pressure contact electrode to record the monophasic action potential (MAP) from the left ventricular epicardium. At completion of coronary grafting the MAP was recorded with grafts open and then during a short period of occlusion in the paced working heart. At the time of writing 17 patients have been studied. In all patients MAP recordings demonstrated typical ischaemic changes, that is reduction in diastolic potential, amplitude, and duration. These changes were apparent within a few seconds of occluding the grafts and the MAP was monitored for up to 90 s. Opening the grafts reversed these changes. The cases included various combinations of IMA and vein grafts.

The method provides an instantaneous index of myocardial revascularisation and an index of the efficiency of individual grafts.

Residual ischaemia and risk of further cardiac events in survivors of first Q and non-Q-wave infarction

S Campbell, D E Jewitt
Cardiac Department, King's College Hospital, London

Non-Q-wave infarction may represent an unstable state with a high risk of future ischaemic events compared with Q wave infarction. We therefore examined a frequency of ischaemic responses and outcome in 137 consecutive survivors of a first myocardial infarction who underwent submaximal treadmill exercise testing 9 4 (2 6) days after infarction. Infarcts were designated as Q wave in 122 and non-Q-wave in 15 patients; the mean peak creatine kinase concentrations were 970 (573) *vs* 459 (278) IU/l respectively ($p<0\cdot001$). Patients were of similar age in both groups (54 3 (6 7) *vs* 55·5 (4·7) years) (NS) and exercised to a similar double product (16 7 (4·7) *vs* 16·1 (4·7) $\times$ 10^3 beats/min $\times$ mm Hg) (NS). Of the Q wave patients 56 (46%) had ST depression $\geqslant 1$ mm compared with three (20%) of the non-Q-wave patients (NS). The frequency of angina was also similar (15% *vs* 13%) (NS). 33·2 (5) days after infarction 110 of the 137 patients underwent radionuclide ventriculography. The mean resting left ventricular ejection fraction in the Q wave group was 50 (13)% *vs* 58 (9)% in the non-Q-wave group ($p<0\cdot05$). During cold pressor stress in 102 patients, 39% of the Q wave patients and 36% of non-Q-wave patients had a fall in ejection fraction of $\geqslant 5\%$ (NS). Adequate follow up for a median period of 27 months (range 12–50) was available for 125 (91%) patients; 23% of the Q wave group had a further cardiac event (death, reinfarction, coronary bypass surgery, unstable angina, cardiac failure) compared with two (15%) in the non-Q group (NS).

Thus first non-Q-wave infarcts are less extensive than Q wave infarcts and survivors do not appear to be in an unstable state with a high risk of further events.

Observations during percutaneous transluminal coronary angioplasty with synchronised coronary sinus retroperfusion

K J Beatt, P J de Feyter, P D Verdouw,
P G Hugenholtz, P W Serruys
Thoraxcenter, Rotterdam, The Netherlands

Coronary sinus retroperfusion (SRP) has been proposed as a method of improving myocardial perfusion during (PTCA) so that coronary artery occlusion times may be prolonged. In three patients a proximal stenosis of the left anterior descending coronary artery (LAD stenosis) was dilated by PTCA, the balloon dilatations being performed with and without SRP. Patients were selected for the study if they had easily provoked angina pectoris, a proximal LAD lesion with a large area of potentially ischaemic myocardium, and normal left ventricular anterior wall motion. In order to assess the degree of myocardial ischaemia the following variables were monitored during coronary artery occlusion, both before and during SRP: time to onset of chest pain, surface and intracoronary ECGs, left ventricular pressure, and the pressure derived indices, dP/dt, Vmax, and time relaxation constants. In addition, the first 20 min period of SRP was monitored to assess any haemodynamic consequence of this method of perfusion. Coronary occlusion times during PTCA varied from 45 to 174 s.

In all three patients SRP was feasible with no evident adverse effects. No change was seen in left ventricular haemodynamic function during 20 min of control SRP. During coronary artery occlusion the time to onset of chest pain and ST segment change as well as the ischaemia related haemodynamic changes showed no improvement with coronary sinus retroperfusion.

Percutaneous transluminal coronary angioplasty for recurrent angina pectoris after coronary artery surgery

British Coronary Angioplasty Group
Collator: A A McLeod, Cardiac Department,
King's College Hospital, London

The efficacy and safety of percutaneous transluminal coronary angioplasty (PTCA) for new or recurrent stenoses in native coronary vessels and saphenous vein aortocoronary grafts in patients who had undergone previous coronary artery bypass grafting (CABG) were reviewed. Ninety procedures were performed in 79 patients. One hundred and twelve vessels were attempted (47 grafts and 65 native vessels) Success defined as 50% improvement in stenosis diameter with improvement in symptoms was obtained after 72 (80%) of the 90 procedures. Successfully dilated lesions were reduced from 86 (8) (SD)% to 30 (14)% in diameter. Three patients had the left main coronary artery successfully dilated. Narrowing of the distal anastomosis was successfully dilated in 88% of grafts, but this was not significantly different from overall success rate Major complications were: deaths (0); myocardial infarction (2); and emergency CABG (1). Elective CABG was subsequently performed in nine (10%) patients. Three of these patients died at operation. Overall operative mortality for repeat CABG (three United Kingdom units) is 6/91 (7%). This differs from PTCA experience (0/90; $p<0.02$). Of 55 patients in whom accurate follow up data is known, those experiencing recurrent symptoms had a median improvement time of three months (range 1–24, n = 12). Patients with reduced or absent symptoms have a median follow up of 11 months (range 1–69, n = 43).

These results suggest that PTCA has an important palliative role in patients whose symptoms recur after CABG.

Success and complication rates in patients with unstable angina undergoing coronary angioplasty

R A Perry, A Singh, M F Shiu
Department of Cardiovascular Medicine,
Queen Elizabeth Hospital, Birmingham

To examine whether coronary angioplasty in patients with unstable angina is associated with a higher complication rate, we studied 184 consecutive patients undergoing primary coronary angioplasty. Sixty four had unstable angina (group A) In these patients the primary success rate was 84%, which was no different from that in 120 patients with chronic stable angina (group B). Failure in group A was due to failure to cross in four cases, acute myocardial infarction in five with one death. Failure in group B was due to failure to cross in 11 and acute myocardial infarction in eight. In group A 45% of patients had had a previous myocardial infarction and in this subgroup the failure rate was 24% compared with 8% in patients with no infarction; this excess failure rate was mainly due to an increase in major complications. In group B 40% of patients had had previous infarction and the failure rate in these patients was similar to those in group A (25%), again mainly due to an increase in the major complications.

In this series the success of angioplasty in patients with unstable angina was similar to that in patients with stable symptoms. Failure in patients with unstable angina was more likely to be due to a major complication than failure to cross the lesion The presence of previous infarction significantly reduced the success rate in patients undergoing angioplasty whether this was for unstable or stable symptoms

Does invasive cardiology require the presence of cardiac surgery?

J Bayliss, C Shakespeare, C Lincoln, R Sutton
Westminster Hospital, London

The demand for invasive cardiology is increasing, and some departments perform procedures such as angiography and percutaneous transluminal angioplasty (PTCA) in the absence of on-site facilities for cardiac surgery. In June 1985 our cardiac surgical unit was closed; invasive procedures are still performed, but patients requiring surgery are now referred to the Brompton Hospital. We have compared the workload for the years before and after the closure of our surgical unit, to assess its impact. In the 12 months before closure 353 angiographic procedures were performed (including 6 PTCA, plus 6 transvenous His bundle ablations) without complication. 133 (38%) patients were referred for surgery, 93 of them required coronary artery bypass grafts (CABG). In the 12 months after closure, 286 angiographic procedures were performed (6 PTCA and 4 ventricular biopsies, plus 3 His ablations) without complication. 146 (51%) patients were referred for surgery, 114 of them required CABG. The provision of emergency surgery was not affected by closure of our unit; before the closure one patient required emergency surgery immediately after angiography and the delay until cardiac bypass was 3 hours, whereas after closure this delay was 2·45 and 3 hours in two patients who had to be transferred to the Brompton. The delay until urgent surgery, however, increased from a mean of 4 days (range 1–7, n = 28) to 16 days (1–54, n = 33) ($p<0.0001$), and three patients died awaiting urgent surgery after closure. The delay until routine surgery increased from 30 days (8–98, n = 104) to 80 days (8–203, n = 108) ($p<0.0001$).

These results indicate that it is safe to perform invasive cardiac procedures, and in selected cases PTCA also, without on-site cardiac surgical backup; close cooperation with the surgical centre is essential. The loss of surgical facilities has caused a deterioration in overall cardiac service, with far longer delays for urgent and routine cases.

Incidence and time to restenosis after percutaneous transluminal coronary angioplasty

K J Beatt, R Geuskens, J E Luijten, P G Hugenholtz, P W Serruys
Thoraxcenter, Rotterdam, The Netherlands

Current data suggest that restenosis (RS) after percutaneous transluminal coronary angioplasty (PTCA) occurs within the first eight weeks. To assesses the true incidence and time to restenosis we reinvestigated three consecutive groups of 100 patients at 30, 60, and 90 days after PTCA. The diameter stenosis (DS) was analysed quantitatively by an automated edge detection and the results were expressed according to six different proposed criteria for restenosis—four from the National Heart, Lung and Blood Institute (30% increase in DS, <50% to <70% increase in DS, increase in DS by 10%, loss of 50% of gain of DS after PTCA) and two from the Thoraxcenter (from <50% to >50% DS, decrease in diameter ≥0 36 mm). For the group analysed at 30 days after PTCA the incidence of RS was between 2% and 16%, for those analysed at 60 days it was between 4% and 22%, and for those analysed at 90 days it was between 2% and 47%. We conclude that (*a*) although most patients who develop restenosis can be identified at 60 days the number is still increasing at 90 days, (*b*) the incidence of restenosis varies considerably depending on the angiographic definition used and this should always be precisely documented, and (*c*) a method of quantitative angiographic assessment is necessary to obtain meaningful data.

Applicability of percutaneous transluminal coronary angioplasty to patients presenting with unstable angina

P Quigley, P Gishen, G Jackson, D E Jewitt
Cardiac Department, King's College Hospital, London

Increasing evidence suggests a therapeutic role for urgent PTCA in patients with unstable angina. To investigate the applicability of PTCA in this condition 94 patients presenting with unstable angina in whom coronary arteriography was indicated were prospectively studied. Particular attention was paid to risk factor profiles, previous history of infarction or angina, and angina patterns on admission (crescendo, rest pain, transient electrocardiographic changes) as possible predictors of suitability for PTCA. Angiograms were reviewed by three independent observers. Unsuitable criteria for PTCA included mainstem disease, diffuse disease, major side branch involvement, longstanding occlusion, difficult access, and normal or minimally diseased vessels. Three groups were identified: group 1, totally suitable with all significant stenoses amenable to PTCA, n = 30 (32%) (eighteen had single vessel disease and 12 had two or more vessels involved); group 2, partially suitable with culprit lesion amenable to PTCA, n = 28 (30%); group 3, totally unsuitable with mostly severe diffuse disease, n = 36 (38%). Multiple logistic regression analysis indicated that absence of stable angina or the presence of stable angina for <6 months were influential in predicting subsequent suitability.

Patients with unstable angina who are being considered for angiography have lesions that are frequently amenable to PTCA, particularly in the absence of preceding stable angina. Ideally arteriography should be performed when facilities to proceed directly to PTCA are present. These results should facilitate the design of future trials of PTCA *vs* surgery or medical management in unstable angina.

Can angiotensin converting enzyme inhibitors replace diuretics as sole treatment for mild heart failure?

A Richardson, A J I Scriven, J Parameshwar, J Bayliss, P A Poole-Wilson, G C Sutton
Hillingdon Hospital, Uxbridge, Middlesex, and Cardiothoracic Institute, London

Patients with chronic mild heart failure are usually treated with diuretics which may have adverse long term effects caused by inappropriate stimulation of the renin-angiotensin-aldosterone system. Angiotensin converting enzyme (ACE) inhibition results in more appropriate long term neuroendocrine balance, but is it adequate treatment alone even in mild heart failure? Fourteen patients with mild heart failure (angiographic or echocardiographic left ventricular dysfunction who complained of breathlessness on exertion) and who had been stable for three months on maintenance frusemide 40 mg and amiloride 5 mg (Frumil) daily were studied in a randomised double blind crossover trial. In one two month period captopril 25 mg was given three times a day and in the other Frumil was given once daily. Clinical status, exercise tolerance, and neuroendocrine data were assessed. During captopril treatment four patients were withdrawn because of increasing dyspnoea; two of them had pulmonary oedema. No withdrawals occurred during Frumil treatment ($p < 0.05$). Six of the 14 patients had had pulmonary or peripheral oedema within the previous two years; all four withdrawals occurred in this group, and there were no withdrawals among patients without previous pulmonary oedema ($p < 0.02$). Treadmill exercise time was unaltered by both treatments. There were no differences in body weight, lying and standing blood pressure, heart rate, or concentrations of plasma and urinary electrolytes. During captopril treatment resting noradrenaline fell from 727 to 556 pg/ml (NS), plasma renin activity rose from 2813 to 8466 pg/ml/h ($p < 0.05$), and aldosterone fell from 400 to 143 pmol/l ($p < 0.01$). There were no significant changes during Frumil treatment.

Although favourable neuroendocrine changes occurred in patients with mild heart failure treated with ACE inhibitors in contrast with diuretics, ACE inhibitors alone were inadequate to maintain control of heart failure in those who had recently had pulmonary or peripheral oedema.

Haemodynamic and renal effects of dopexamine in low output heart failure

L B Tan, S A Smith, W A Littler, R G Murray
Cardiology Department, East Birmingham Hospital, Bordesley Green East, Birmingham

Dopexamine is a new dopaminergic agonist which unlike dopamine is devoid of α adrenergic vasoconstrictive effects even at the higher dosages. The haemodynamic and renal effects of dopexamine were studied in 10 patients with low output state ischaemic heart failure (New York Heart Association class IIIb-IV). Haemodynamic data were obtained by means of thermodilution Swan-Ganz catheters and radial arterial cannulas. Graded doses of dopexamine, ranging from 0 to 6 μg/kg/min, were infused over consecutive 20 min periods. Heart rate increased from 86 (16) to a maximum of 100 (14) beats/min ($p < 0.01$). Cardiac index increased from 1·6 (0·5) to a maximum of 2·8 (1·1) l/min ($p < 0.01$). Systemic vascular resistance decreased from 1720 (431) to 1116 (426) dyn.s.cm^{-5} ($p < 0.01$). We used an analytical technique (previously presented to the Society) which enables us to separate inotropic from vasodilatory effects. Eight of the 10 patients showed true positive inotropic response to dopexamine. Improvement in renal function was seen at 4 μg/kg/min in five of the 10 patients, with increases in urine flow rate from 0·7 (0·3) at control to 2·9 (1·1) ml/min, creatinine clearance from 35 (17) to 78 (26) ml/min, and fractional excretion of sodium from 0·35 (0·24) to 1·0 (0·75)%. These improvements did not parallel the observed haemodynamic changes. Those patients who did not improve comprised two who remained anuric throughout and three who had pre-existing irreversible renal failure.

These data suggest that in patients with low output heart failure and renal hypoperfusion dopexamine can produce beneficial systemic and renal vasodilatation in addition to exerting a positive inotropic effect.

Captopril in congestive heart failure: the effects of oxygen consumption in the exercising leg

A D Timmis, L M R Bojanowski, Y Najm, R Gosling
Departments of Cardiology and Ultrasonic Angiology, Guy's Hospital, London

Placebo controlled studies show that captopril, unlike conventional vasodilators, improves exercise tolerance in congestive cardiac failure (CCF). The mechanism of this beneficial effect is unknown. We have examined the effects of captopril on oxygen consumption in the exercising leg by means of Doppler measurements of femoral flow and arteriovenous oxygen difference. Twenty patients with CCF were randomised to captopril 25 mg ($n = 10$) or placebo ($n = 10$). Maximal supine exercise of one leg was performed before and one hour after treatment. Captopril increased stroke index at peak exercise from 26 (8) to 34 (10) ml/beat/m^2 and reduced pulmonary artery wedge pressure from 26 (9) to 16 (10) mm Hg ($p < 0.05$). Exercise time increased from 12·5 (6·3) to 15·5 (11·4) minutes ($p < 0.05$). Despite the improvement in central haemodynamic function and exercise tolerance there was no significant change in peak values for femoral flow (1060 (564) to 942 (421) ml/min) or oxygen consumption (134 (81) to 111 (58) ml/min) in the leg. Cutaneous flow in the leg, as reflected by skin temperature, was also unaffected (29·9 (1·8) to 29·7 (1·7)°C). Repeat studies after 4 weeks' treatment with captopril 25 mg three times a day showed sustained improvement in central haemodynamic function and exercise tolerance but no change in peak oxygen consumption in the leg. In patients randomised to placebo neither central haemodynamic function nor oxygen consumption in the exercising leg altered significantly.

These data confirm that captopril improves central haemodynamic function in patients with CCF. Nevertheless, the effects of this agent on oxygen consumption in the exercising leg are not significantly different from those of placebo. Thus the therapeutic benefits of captopril in CCF are not mediated by improved flow redistribution to exercising skeletal muscle.

Comparison of oral inotropic and vasodilator treatment in the management of severe heart failure

A J Scriven, D Lipkin, J Bayliss, G C Sutton,
P A Poole-Wilson
National Heart Hospital and Hillingdon Hospital, London

Enoximone (MDL 17043) is a phosphodiesterase inhibitor with both positive inotropic and vasodilator properties. It has been shown both in the short term and over a longer term to improve pump function in patients with severe heart failure, but it has not been compared with vasodilatory treatment. Accordingly, 13 patients with severe heart failure (New York Heart Association class III–IV) taking frusemide $\geqslant$80 mg daily were studied in a randomised double blind crossover trial to compare enoximone 150 mg three times a day with captopril 25 mg three times a day. Clinical state, exercise haemodynamic function, and maximal oxygen uptake (Vo_2max) were assessed while the patients were on diuretics alone (control) and one month after the addition of each drug. Two patients withdrew on captopril and one on enoximone. At rest, systemic and pulmonary vascular resistance fell on enoximone ($p<0·02$); these variables were unchanged on captopril and they were not reduced by either drug during exercise. Resting cardiac index was 1·9 l/m^2/min and did not change with either drug treatment. The cardiac index on exercise was 3·7 during the control phase, increasing to 4·4 on captopril ($p<0·02$) and to 4·6 on enoximone ($p < 0·02$). Control exercise treadmill time was 20 min, increasing to 25 min on captopril ($p<0·05$) and 26 min on enoximone ($p<0·02$). Control Vo_2max was 12·6 ml/kg/min; this rose to 15·5 on captopril ($p<0·05$) and to 15·0 on enoximone ($p<0·05$). Although these mean values represent improvement for the group, useful functional improvement occurred in only six patients, who had similar responses to both drugs whereas seven patients showed no response to either drug.

Enoximone, like captopril, produces sustained improvement in exercise capacity and haemodynamic function in some patients with severe heart failure.

An objective assessment of maximal exercise capacity from a submaximal exercise test in patients with chronic heart failure

N P Buller, P A Poole-Wilson
The Cardiothoracic Institute, London

Measurement of oxygen consumption at peak exercise (Vo_2max) is a useful index of severity in the assessment of patients with chronic heart failure. Vo_2max is, however, effort dependent and a true maximal value is only obtained at an uncomfortable level of exercise. To overcome these problems we have fitted the equation $y = ax - bx^2$ to the curve of oxygen consumption (Vo_2) against carbon dioxide production (Vco_2). The relation is a straight line early during exercise and "a" represents the respiratory quotient. The value of "b" reflects the curvature of the relation later in exercise. Once these two constants are known the calculated maximal oxygen consumption is given by $a^2/4b$. To validate this approach we have analysed Vo_2 and Vco_2 data obtained from three healthy volunteers and 11 patients (11 men, 3 women, age range 29–69 years). All subjects underwent maximal symptom limited treadmill exercise testing during which values of Vo_2 and Vco_2 were recorded every 10 s. Calculated Vo_2max ranged from 12 7 to 36·8 ml/kg/min. Measured Vo_2max, expressed as a percentage of the calculated value for each subject, ranged from 85% to 103% (95 8 (5·6)%, mean (SD)), showing good agreement between the two methods. The data were reanalysed using only those values obtained during the first 75% of the exercise test. Calculated Vo_2max was unchanged at 99 6 (7·6)%. This contrasts with a measured Vo_2 at 75% exercise duration of 82·1 (10 1)%. This method is truly objective and allows maximal exercise capacity to be predicted from submaximal exercise tests.

Duration of endocrine and haemodynamic effects of enalapril and captopril in heart failure

A D Flapan, T R D Shaw, S Stewart, E Davies,
B C Williams, C R W Edwards
Western General Hospital, Edinburgh

The duration of effect of single oral doses of enalapril and captopril was studied in 32 patients with heart failure. Haemodynamic recordings were made up to 12 hours after the dose and endocrine changes were followed for 24 hours. Twelve patients received a 20 mg dose of enalapril. Maximum reduction in systemic vascular resistance (SVR) occurred at three hours after the dose and SVR continued to be reduced until 12 hours after the dose. Mean (SEM) plasma angiotensin II concentration fell from 21·3 (4·8) to a nadir of 3·9 (1·6) pmol/l at three hours and remained reduced at 5·1 (1·0) pmol/l ($p < 0·01$) at 24 hours. Captopril 50 mg (5 patients) caused a more rapid reduction in SVR and plasma angiotensin II concentration, but both had returned to near control values at 12 hours. Captopril 75 mg (5 patients) gave more prolonged haemodynamic and endocrine responses but these were again not sustained for 12 hours. Captopril 150 mg produced a maximum fall in SVR of 31% at 30 minutes; at 12 hours SVR was still reduced by 28%. Mean plasma angiotensin II concentration fell from 29·5 (14·05) to 3·3 (0·77) pmol/l at 90 minutes and remained low at 5·1 (1·4) pmol/l at 12 hours, but had risen to 17·8 (6·3) pmol/l at 24 hours.

These data suggest that a 75 mg twice daily dose of captopril may be useful in long term treatment, and subsequent data seem to confirm this.

Myocardial infarction without total coronary occlusion

A D Timmis, B Griffin, J C P Crick, R Henderson, E Sowton
Guy's Hospital, London

Early thrombolytic treatment is now recommended in acute myocardial infarction in order to recanalise the infarct related coronary artery (IRCA). When the IRCA is already patent, however, different therapeutic strategies may be more appropriate. We have reviewed data in 37 patients with acute myocardial infarction who underwent coronary angiography 3·2 (1·2) hours after the onset of chest pain. The angiograms were repeated 90 minutes later. In eight (21%) patients the IRCA was already patent at the first angiogram (group 1) and in a further nine patients who received thrombolytic treatment early recanalisation of the IRCA occurred before the second angiogram (group 2). In the remainder the IRCA remained persistently occluded (group 3). Serial measurements of plasma creatine kinase (CK) confirmed an early peak in groups 1 and 2 compared with group 3 (10·3 (4·8) *vs* 20·7 (6·8) hours after hospital admission, $p < 0·001$). The peak was earliest, however, in group 1, occurring after only 8·0 (3·7) hours, 4·5 hours earlier than in group 2 ($p < 0·05$). Moreover, in group 1 resolution of ST segment elevation was occurring within one hour of hospital admission, compared with two hours in group 2 and six hours in group 3.

These data demonstrate that a significant proportion of patients with acute myocardial infarction have a patent IRCA at the time of hospital admission. In these patients a very early peak in plasma CK and rapid resolution of ST segment changes occur. Identification of this important subgroup may permit development of specific treatment strategies to prevent progression to total coronary occlusion.

Ventricular septal defect complicating myocardial infarction: is early surgery justified?

M Norell, A Gershlick, R Pillai, P Magee, R Balcon
The London Chest Hospital, London

In an attempt to improve outcome, early surgery has been advocated for ventricular septal defect (VSD) complicating myocardial infarction. To examine the justification for this approach a consecutive series of 55 such patients were reviewed of whom 40 underwent surgical repair. Those presenting before 1982 (group 1, $n = 18$) were compared with those presenting after 1982 (group 2, $n = 22$), when a policy of early surgical intervention was adopted. The mean interval from VSD to surgery was 53 days in group 1 and 10 days in group 2 ($p < 0·05$). Preoperatively, cardiogenic shock was more frequent in group 2 than in group 1 (45% *vs* 11%, $p < 0·05$) and both plasma urea and creatinine were higher (16 *vs* 11 mmol/l ($p < 0·05$) and 198 *vs* 114 μmol/l ($p < 0·01$) respectively). Patients in group 2 also had a lower systolic blood pressure (96 *vs* 106 mm Hg), a higher incidence of poor peripheral perfusion (68% *vs* 44%), and a more frequent need for intra-aortic balloon pump support (41% *vs* 22%); these differences did not reach statistical significance, however. Despite patients in group 2 being more haemodynamically compromised, their surgical mortality was not significantly different from that in group 1 (7 *vs* 3 patients). Early surgical repair of VSD complicating myocardial infarction is frequently undertaken in critically ill patients. The surgical risk is, however, not significantly increased and such patients, whose prognosis is otherwise poor, may be salvaged.

Effect of nifedipine in the early phase of acute myocardial infarction on enzymatically estimated infarct size and arrhythmias

Linda Walker, G MacKenzie, Jennifer Adgey
Regional Medical Cardiology Centre and Queen's University of Belfast, Belfast

In a double blind placebo controlled trial 434 patients with suspected myocardial infarction (MI) were randomised within 6 hours from the onset of suspected MI to treatment with nifedipine (n = 217) placebo (n = 217). During the treatment period of 48 hours a 10 mg capsule containing nifedipine or placebo was administered sublingually every four hours for 24 hours and then orally every four hours for the next 24 hours. Acute MI was confirmed in 295 patients (146 had nifedipine and 149 had placebo). The median time to intervention in patients with acute MI was 111 min for those receiving nifedipine and 129 min for those receiving placebo. Withdrawal from the study was necessary in 13 patients with MI in the nifedipine group and in 12 in the placebo group. MI size was estimated from the release of creatine kinase isoenzyme MB (CK–MB) and creatine kinase (CK) by applying Norris's formula to the results of blood samples taken every four hours for 48 hours. Total CK–MB released was 406·4 (27·2) IU/l (mean (SEM)) in the nifedipine group and 345 7 (20·5) IU/l in the placebo group. Total CK released was 2749·6 (165·1) IU/l in the nifedipine group, and 2698·4 (145·9) IU/l in the placebo group. Arrhythmia analysis of 24 hour tapes during the 48 hour treatment period showed no significant difference between the nifedipine and placebo groups in the incidence of ventricular extrasystoles, consecutive extrasystoles, self-terminating ventricular tachycardia, sustained ventricular tachycardia, or ventricular fibrillation. Ventricular fibrillation occurred during the 48 hour study in four (3·8%) patients in the nifedipine group and in 9 (7 5%) patients in the placebo group. In hospital mortality was 7 (6 6%) in the nifedipine group and 7 (5·8%) in the placebo group.

Treatment with nifedipine in the early phase of acute MI appears to have no effect on limitation of enzymatically estimated MI size, incidence of ventricular arrhythmias, or in hospital mortality.

The spectrum of right ventricular dysfunction associated with inferior myocardial infarction

I McGhie, Ann C Tweddel, W Martin, I Hutton
University Department of Medical Cardiology,
Royal Infirmary, Glasgow

Right ventricular dysfunction after inferior myocardial infarction can have potentially serious consequences, which may be remediable with the appropriate therapeutic manoeuvres. The aim of this study was to define the spectrum of right ventricular dysfunction occurring during the early stages of inferior myocardial infarction and also to relate this to clinical evidence of right ventricular dysfunction. Twenty six patients with acute inferior myocardial infarction were studied. Right ventricular function was obtained by a gated xenon technique. Right ventricular ejection fractions (RVEF) ranged from 7 to 54% with a mean 30 (11)%. The normal range for this technique, obtained from 21 volunteers, is 35–55% (mean 43 (15)%). Thirteen patients (50%) had clinical features indicative of right ventricular dysfunction and in these patients RVEF ranged from 7 to 54% (mean 26 (11)%), which is significantly less than normal. In the remaining patients who displayed no evidence of right ventricular dysfunction the RVEF ranged from 16 to 49% (mean 35(9)%). If the patients were subdivided on the basis of the RVEF, with a RVEF <35% being indicative of significant right ventricular dysfunction, the clinical signs had a sensitivity of 72% (13/18), a specificity of 87·5% (7/8), and a predictive accuracy of 76% (20/26).

In conclusion, these results show that inferior myocardial infarction results in a wide spectrum of right ventricular dysfunction and that the presence of right ventricular dysfunction may not manifest itself clinically.

Epicardial ECG as an indicator of myocardial ischaemia and dysfunction during coronary angioplasty

I Amende, G Herrmann, R Simon, P R Lichtlen
Medical University Hannover, Hannover, Federal Republic of Germany

Monitoring of the epicardial electrocardiogram (epi-ECG) by connecting the end of the intracoronary guidewire to the V lead provides a simple method of detecting myocardial ischaemia during percutaneous transluminal coronary angioplasty (PTCA). To assess the extent to which changes in the epi-ECG reflect ischaemia induced left ventricular (LV) dysfunction we simultaneously recorded the epi-ECG and the pulmonary wedge pressure (PWP) during 323 balloon inflations (BI) in 114 patients. Eighty one patients had stenoses of the anterior descending, 18 of the right, and 15 of the circumflex coronary artery. ST elevation or depression ⩾1 mV in the epi-ECG during BI was assumed to indicate significant myocardial ischaemia and a rise in PWP ⩾5 mm Hg to reflect LV dysfunction. During 163 BI there was a change in both PWP and epi-ECG; during 45 BI neither changed. The PWP rose during 21 BI without ischaemic signs in the epi-ECG. There was no change in PWP during 94 BI despite alterations in the epi-ECG. Thus epi-ECG changed in 80% (257/323). As a reflector of a rise in PWP, changes in the epi-ECG had a sensitivity of 89% and a specificity of 32%. Increasing ST elevation in the epi-ECG with little change in PWP heralded acute closure in three patients immediately after PTCA. The guidewire facilitated redilatation of the vessel.

We conclude that the epi-ECG is sensitive but non-specific in detecting myocardial ischaemia during PTCA and aids in recognition of impending acute occlusion immediately after PTCA.

Management of coronary artery occlusion occurring at coronary angioplasty

C J Foster, W C Brownlee, H G Love
Department of Cardiology, Manchester Royal Infirmary, Manchester

Occlusion of a coronary artery at or shortly after coronary angioplasty is an accepted risk of this procedure. The correct management of this complication is not clear, especially if the patient has left the catheter room. The decision is usually between surgery and reopening the occlusion by coronary angioplasty. Of 98 patients (111 arteries) undergoing non-urgent angioplasty total occlusion occurred in 13 patients (14 arteries). In five this occurred after they had left the catheter room. One patient with good collateral supply to the occluded vessel had no evidence of infarction and had elective surgery. In the remaining 12 an attempt was made to cross and open the occlusion; this was successful in 11. In three of these the artery became reoccluded and the patients went for urgent surgery (one with two arteries occluded). Only two of these patients had evidence of infarction postoperatively. Of the eight patients in whom the artery was successfully reopened only one had ECG or enzyme evidence of a small infarct. In the patient in whom the attempt to cross the occlusion failed there was good collateral circulation to the occluded vessel and no evidence of infarction. This patient underwent elective surgery.

These results demonstrate that it is possible to reopen most vessels occluded at coronary angioplasty and suggest that, provided that the initial angioplasty was not technically difficult and a good result was obtained, repeat angioplasty should be attempted. This management should significantly reduce the number of patients requiring urgent surgery.

Determinants of left ventricular function one year after cardiac transplantation

C J Reid, S Qureshi, M Yacoub
Harefield Hospital, Harefield, Middlesex

In 107 consecutive patients the effect of certain patient related factors (recipient age and sex, type of immunosuppression, and frequency of acute rejection) and of patient unrelated factors (donor age and sex and ischaemia time) on left ventricular ejection fraction (LVEF) measured by radionuclide angiography were assessed one year after cardiac transplantation. Resting LVEF in recipients aged <20 years was 74·4 (4·51)% (mean (SEM)) and in those aged 40 to 60 years it was 61·7 (1·41)% (p < 0·01). On exercise it was 81·25 (5·9)% and 68·7 (1·24)% (p < 0·01) respectively. In patients receiving cyclosporin and azathioprine resting LVEF was 64·7 (1·36)% and in those on prednisolone and azathioprine it was 57·3 (2·81)% (p < 0·05). On exercise LVEF was 70·16 (1·48)% and 62·30 (3·47)% (p < 0·05) respectively. Though there was a trend for lower donor age, shorter duration of ischaemia time, and smaller number of acute rejection episodes in the first year to be associated with a higher LVEF both at rest and on exercise, this difference was not statistically significant.

It is concluded that radionuclide angiography is a useful method for assessing the influence of various factors on LVEF at one year after cardiac transplantation and that the type of immunosuppression and recipient age have the most significant effect.

Cardiac transplantation in severely ill patients requiring active in hospital support

D Mulcahy, Christine Wright, Lorna Mockus, M Yacoub, K M Fox
National Heart Hospital, London

Thirty two patients were accepted for cardiac transplantation from a single unit at the National Heart Hospital between October 1984 and December 1985. Fourteen patients were fully investigated and were discharged home to await a suitable donor. Eighteen patients were referred for urgent cardiac transplantation. All required active in hospital intervention in the form of intravenous infusions of cardiac drugs, and also intra-aortic balloon counterpulsation, peritoneal dialysis, temporary cardiac pacing, and assisted ventilation as required in order to sustain life. Of these 18 severely ill patients, four died while awaiting a suitable donor and 14 received a cardiac transplant. There were four deaths within 24 hours of operation, and 10 patients had a successful outcome to surgery. There was one late death 10 weeks after surgery. Nine patients are alive and well 16–69 weeks after cardiac transplantation. Severe renal dysfunction was associated with a poor eventual outcome in this group. Despite difficulties in maintaining strict selection criteria when these patients were considered for cardiac transplantation, and a shortfall in the number of suitable donor hearts, we feel that a successful outcome to surgery in over 50% of a group of patients who would otherwise all have died while in hospital justifies this form of treatment in these terminally ill patients.

Exercise capacity and heart rate response to dynamic exercise one year after combined heart and lung transplantation

N Banner, A Khaghani, Catherine O'Brien,
A Mitchell, M Yacoub
Harefield Hospital, Harefield, Middlesex

Eight heart lung transplantation (HLT) recipients who had survived one year after operation were exercised according to the Bruce treadmill protocol to study their exercise capacity, ECG, and blood pressure response to dynamic exercise. Eight orthotopic cardiac transplant (CT) recipients matched for age, sex, and time after operation were studied as controls. All patients received cyclosporin and azathioprine immunosuppression. One CT and two HLT patients were taking hydralazine and one CT patient was on methyldopa and labetalol. Chest *x* ray, cardiac catheterisation, and endomyocardial biopsy were used to exclude rejection and document any coronary artery disease. All data are given as means followed by standard deviation. HLT patients were 30·6 (11·6) years old and CT patients 32·4 (13·1) years. Resting ECGs showed complete right bundle branch block in one and partial right bundle branch block in two HLT patients; four CT patients had complete right bundle branch block. Resting heart rate was 102 (14) in HLT patients and 105 (14) beats/min in CT patients (NS). The heart rate at maximum exercise was 144 (18) for the HLT group and 142 (17) beats/min for the CT group (NS) and exercise duration was 10 (2·1) min for the HLT group and 9·6 (1·7) min for the CT group (NS). All patients stopped because of exhaustion or leg muscle fatigue. Systolic blood pressure at rest was 123 (15) mm Hg in the HLT group and 110 (16) mm Hg in the CT group (NS). Values at peak exercise were 164 (25) mm Hg and 136 (21) mm Hg respectively ($p < 0{\cdot}05$). One HLT patient developed T wave inversion and ST depression in the inferolateral leads during exercise. No other ECG changes occurred. The heart rate response accelerated and declined slowly in both groups in a pattern that was compatible with autonomic denervation. Exercise capacity one year after HLT is good and resembles that after cardiac transplantation.

Changes in Doppler and M mode echocardiographic indices of left ventricular function during acute cardiac allograft rejection

H A Valantine, P J Oldershaw, M B Fowler,
D G Gibson, L Hatle, S A Hunt, M E Billingham,
E B Stinson, R L Popp
Brompton Hospital, London; and Stanford
University California, USA

Changes in left ventricular (LV) systolic function only appear late in cardiac allograft rejection and abnormalities in diastolic function have been suggested as sensitive markers of acute rejection. To evaluate this hypothesis changes in Doppler indices of LV ejection and filling were compared with posterior wall dimensions and their rates of thickening and thinning during acute rejection. Serial Doppler and M mode studies were performed in six transplant recipients within six hours of myocardial biopsy on eight separate occasions in each patient. Flow velocities across the mitral and aortic valves were recorded by continuous wave Doppler ultrasound. M mode echocardiograms of the LV cavity were recorded and digitised for analysis of dimensions and their rate of change during systole and diastole. Measurements were performed without knowledge of the biopsy findings, which were graded as normal or rejection with myocyte necrosis. Compared with normal results rejection with myocyte necrosis was associated with a shorter isovolumic relaxation time (73·1 (12·5) *vs* 59·4 (4·5) ms, $p \leqslant 0{\cdot}0005$), increased early mitral flow velocity (0·625 (0·045) *vs* 0·92 (0·099) m/s, $p \leqslant 0{\cdot}0005$), and a shorter pressure half time (83·5 (4·7) *vs* 62 (3·2) ms, $p \leqslant 0{\cdot}0005$). These changes were accompanied by an increase in posterior wall diastolic dimension (1·06 (0·09) *vs* 1·3 (0·75) cm, $p \leqslant 0{\cdot}05$), a decrease in the rate of posterior wall thinning (9·7 (0·8) *vs* 7·7 (0·7) cm/s, $p \leqslant 0{\cdot}025$), and normalised rate of posterior wall thinning (7·25) (0·36) *vs* 5·4 (0·68) s, $p \leqslant 0{\cdot}05$). In contrast, there were no significant changes in indices of LV ejection (peak aortic velocity, ejection time, rate of posterior wall thickening).

These changes confirm that abnormal diastolic function may be a marker for the monitoring of acute allograft rejection.

Haemodynamics and lung function one year after combined heart lung transplantation

N R Banner, A Khaghani, A G Mitchell,
R Radley-Smith, P Lockwood, M H Lloyd,
M Yacoub
Harefield Hospital, Harefield, Middlesex

Eight adolescent and adult patients (mean age 30·5 years, range 15–47) were reinvestigated one year after heart lung transplantation (HLT). Three had primary pulmonary hypertension, four had Eisenmenger's syndrome, and one had emphysema secondary to α_1 antitrypsin deficiency. The mean donor age was 24·3 years (range 21–35), the mean ischaemic time was 45 minutes (range 28–80). Cardiac catheterisation and full pulmonary function testing were performed. All data are quoted as mean (SD). The pulmonary artery pressures were: systolic 20 (5); diastolic 9 (2), and mean 13 (2) mm Hg. The pulmonary capillary wedge pressure was 8 (2) mm Hg. The aortic pressures were: systolic 135 (17), diastolic 84 (13), and mean 107 (17) mm Hg. The left ventricular pressures were: systolic 137 (20) mm Hg and diastolic 9 (2·4) m Hg. The mean cardiac output was 6·1 (1·3) l/min. The pulmonary vascular resistance was 0·9 (0·6) units. Angiography showed a left ventricular ejection fraction of 84 (9·2)%. All eight patients had coronary mediastinal collaterals. None had accelerated coronary artery disease. Arterial oxygen tension was 12 8 (0·7) kPa and arterial Pco_2 was 4·9 (0·5) kPa breathing air, forced expiratory volume in 1 s was 3·35 (0·94) l (mean 126% of predicted), forced vital capacity 3·89 (0·8) l (mean 107% of predicted), total lung capacity 5·69 (1·25 l (mean 123% of predicted), transfer factor 25·3 (6·6) l/min/mm Hg (mean 74% of predicted), transfer coefficient 4·88 (0·79) l/min/mm Hg/l (mean 84% of predicted).

Combined heart lung transplantation with cyclosporin and azathioprine immunosuppression provides good cardiopulmonary function in survivors one year after transplantation.

Efferent autonomic reinnervation after heterotopic cardiac transplantation in humans

A G Mitchell, M Yacoub
Harefield Hospital, Harefield, Middlesex

Reinnervation of the donor heart has not been seen in humans but may occur in dogs. The heart rate changes in donor and recipient hearts after heterotopic ("piggy-back") cardiac transplantation in man in response to parasympathetic and sympathetic stimuli have been analysed. In six patients the donor hearts have shown evidence of reinnervation 1–3 years postoperatively. The resting rate was greater in the donor hearts (mean 88 beats/min) than the recipient hearts (mean 75 beats/min). All reinnervated donor hearts had slower rates than when they were examined six months after operation but this change was not significantly different from changes in the recipient heart. All six patients showed an abrupt decrease of cardiac cycle length on standing (mean −114 ms) and an increase of cycle length with carotid sinus massage (mean +125 ms). These changes were similar in magnitude and time course to changes in the recipient heart. Atropine produced an increase in heart rate in both donor (mean 91 rising to 110 beats/min) and in recipient hearts (mean 80 rising to 95 beats/min). The donor heart remained faster than the recipient heart in five cases. The rate change occurred within one minute of atropine infusion and was accompanied by abolition of changes with posture and carotid sinus massage. Glyceryl trinitrate induced hypotension produced an abrupt increase in heart rate in the donor heart (mean increase 14 beats/min) similar to changes in the recipient heart. Atropine failed to block this response in the single case tested. During exercise testing the donor hearts accelerated faster than in denervated controls and the decline occurred within 1 minute of the end of exercise. At least 75% of the fall of rate occurred within 3 minutes compared with 16% in controls. Rapid glyceryl trinitrate induced tachycardia is considered to be a sympathetic neurogenic response, whereas rate changes with posture or carotid sinus massage are mediated by the parasympathetic system.

Contrary to previous experience reinnervation may develop in man after heterotopic cardiac transplantation.

Percutaneous laser recanalisation of coronary arteries in man: early results

F Crea, G Davies, W J McKenna, M Pashazadeh,
P Kidner, K M Taylor, A Maseri
Royal Postgraduate Medical School, Hammersmith Hospital, London

Percutaneous laser irradiation of coronary arteries by means of bare optical fibres results in perforation because of the difficulty of controlling beam direction in tortuous vessels. We have previously demonstrated in live dogs that this problem can be overcome by use of optical fibres fitted with a metal cap that prevents the forward projection of the laser beam and allows a precisely targeted thermoablation of arterial tissue. We have now attempted percutaneous laser recanalisation of coronary arteries in two patients with refractory angina pectoris and multivessel disease referred for coronary bypass grafting: both patients had a severe proximal stenosis of the left anterior descending artery (LAD). To minimise the effect of potential complications the procedure was attempted at the time of surgery. After pericardiotomy a 9F guiding catheter was introduced via the femoral artery into the left coronary ostium. Through this catheter a 0·012 inch guidewire was advanced across the LAD stenosis. A 1·5 mm metal capped optical fibre coupled to an argon laser was then advanced along the wire to the stenosis. In patient 1 a 3 cm long 70% LAD stenosis was recanalised with a series of four laser irradiations (total energy 252 J) while the fibre was either advanced or withdrawn through the lesion. In patient 2 despite a series of three laser irradiations (total energy 192 J) the fibre did not cross a 3 cm long 90% LAD stenosis and caused coronary perforation. All diseased coronary arteries, including the LAD, were finally grafted.

Thus transluminal laser recanalisation of coronary arteries with metal capped optical fibres is feasible. Further studies in patients undergoing coronary artery bypass surgery are warranted for better definition of the role of this technique and to reduce the risks.

Reduction of vessel wall perforation by the use of sapphire tipped optical fibres in laser angioplasty

T J Bowker, F W Cross, S G Bown, A F Rickards
National Heart Hospital and University College Hospital, London

One approach to reducing the risk of vessel wall perforation due to intravascular laser delivery is to modify the distal tip of the laser fibre. We have compared a bare tipped optical fibre with an optical fibre fitted with a bullet shaped sapphire tip for the transluminal delivery of Nd-YAG laser energy to atheromatous lesions in 33 fresh human postmortem femoral arteries within an artificial blood circulation. With both types of fibre tip the laser delivery system was introduced into the vessel via a standard 9F introducer and the fibre was advanced under radiographic screening to the lesion. Pre-laser and post-laser angiograms and blood flow rates through the vessel were recorded. Laser energy was delivered 5 J at a time until vessel recanalisation or perforation occurred. Angiograms were repeated after each 50 J was delivered. There were seven control vessels (3 occlusions and 4 stenoses) in which mechanical recanalisation without laser energy was unsuccessful. Of the 14 lesions attempted with the bare fibre tip, laser perforation occurred in nine vessels (64%). Recanalisation was achieved in one of the seven occlusions (with 400 J and a post-laser flow rate of 40 ml/min) and in one of the seven stenoses (with 250 J, but no improvement in flow rate). There was no vessel perforation of the 12 lesions attempted with the sapphire tip. Seven out of eight occlusions (2–15 mm in length) were recanalised with a mean energy of 370 J (100–1640 J) and a mean post-laser flow rate of 54 ml/min (32–126 ml/min). There was radiographic improvement in all four stenoses, but the mean flow rate rose from 46 to only 52 ml/min (12% increase).

The use of modified laser fibre tips appears to be an important step towards eliminating the risk of vessel wall perforation in laser angioplasty.

Experimental studies to assess feasibility of laser myotomy

W J McKenna, G J Davies, F Crea, M Pashazadeh, Sally Allwork, P Kidner, A Maseri
Hammersmith Hospital and St Mary's Hospital, London

In hypertrophic cardiomyopathy surgical myotomy/myectomy may improve symptoms but is associated with a significant perioperative mortality (>10%). We have evaluated the feasibility of non-surgical myotomy in a canine model using an argon laser with energy peaks at 488 and 514 mm, a 300 μm core optical fibre fitted with a 1·5 mm metal cap, and a conventional catheter delivery system. Nine anaesthetised greyhounds (25–30 kg) were catheterised through a carotid cutdown using an 8F sheath catheter, which was advanced under fluoroscopy toward the apex of the left ventricle. The fibre tip was attached to a 0·038 steerable guidewire; this was advanced within the catheter so as to be exposed 2 cm from the tip. Appropriate orientation of the fibre toward the anterolateral free wall and anterior septum was achieved with the steerable guidewire; adequate contact between the tip of the fibre and the myocardium was monitored by cross sectional echocardiography and fluoroscopy. The laser was activated (12 W for 30–40 s) while the catheter and optical fibre (under fluoroscopic control) were withdrawn from the base of the anterior papillary muscle to the outflow tract. The animal was then killed and the heart was examined to measure the extent and distribution of the thermal effects of the laser. Heart weights were 285–375 g (median 335 g). Myotomy of the anterior or posterior septum (2·5–4·0 cm length, 1–2 mm width, and 3–5 mm depth) was successful in all nine hearts; in seven there was no damage to other cardiac structures while in two the myotomy was begun too low and had damaged the posterior papillary muscle.

Thus in an animal model of left ventricular hypertrophy a myotomy similar to that achieved in early successful surgical experience can be performed safely, percutaneously by laser. Assessment in patients is now warranted.

Percutaneous transluminal coronary angioplasty in patients with previous coronary artery bypass graft surgery

N Ineson, I C Cooper, M M Webb-Peploe
Department of Cardiology, St Thomas' Hospital, London

Coronary artery bypass graft surgery (CABG) must be viewed, in the light of late graft occlusion and the progression of atherosclerosis in native coronary arteries, as a palliative treatment for angina pectoris. Repeat CABG carries a higher operative risk than initial surgery. At St Thomas' Hospital 40 patients with a history of previous CABG underwent a total of 46 percutaneous transluminal angioplasty (PTCA) procedures in which dilatation of 95 lesions was attempted. In 20 (50%) patients all attempted lesions were successfully dilated. In 12 (30%) patients successful dilatation was achieved in some but not all attempted lesions. In eight (20%) patients no lesion was dilated. Five of the six repeat procedures were successful. Of the 95 lesions attempted 71 (75%) were successfully dilated. There was no difference between the rate of successful dilatation in grafted or ungrafted native vessels and graft stenoses. Restenosis has occurred in 16 (40%) of the lesions restudied. Treadmill exercise tolerence was improved in 68% of patients assessed at 6 weeks after successful PTCA. In 15 (60%) of the 25 patients restudied at 6 months the New York Heart Association class had improved. Improvement in both exercise tolerance and symptoms occurred in patients with partially as well as in those with totally successful procedures. Three patients in this series sustained myocardial infarction; none underwent emergency CABG and there were no deaths.

We conclude that PTCA may be useful in the treatment of patients with recurrent angina after CABG.

Improvement in left ventricular function after successful coronary angioplasty in patients with and without previous myocardial infarction

R A Perry, A Singh, S Chandler, R G Murray, M F Shiu
Department of Cardiovascular Medicine, Queen Elizabeth Hospital, Birmingham

The potential for improvement of left ventricular function by coronary angioplasty may be limited in patients with previous myocardial infarction. We performed rest and exercise ^{99m}Tc left ventriculography and ^{201}Tl perfusion scans on 52 patients before and after successful coronary angioplasty. Fourteen patients had had a previous myocardial infarction (group A) and 38 had angina only (group B). Before angioplasty, group A had lower resting and exercise ejection fraction (47·1 (15·5) and 38·6 (10·8)%) compared with group B (56·3 (8·9) and 51·9 (12·3)%). After angioplasty in both groups the exercise but not the resting ejection fraction improved significantly ($p < 0{\cdot}01$), with the greatest improvement in group A (51·8 (12·2)%) compared with group B (58·8 (10·3)%). There was a significant ($p < 0{\cdot}01$) improvement in exercise thallium score in group A (12·2 (6·5) *vs* 7·1 (5·3)) and group B (5·6 (2·4) *vs* 1·1 (1)). The four hour perfusion score was also improved in group B (2·1 (1·1) *vs* 0·6 (0·9)).

Patients with previous myocardial infarction have a lower resting and exercise ejection fraction with a degree of reversible ischaemia comparable to patients with angina only. In the presence of demonstrable reversible ischaemia patients with previous infarction show a more striking improvement in left ventricular function.

Detection of myocardial ischaemia during coronary angioplasty: limitation of ECG monitoring

M Norell, J Lyons, J Gardener, C Layton, R Balcon
The London Chest Hospital, London

ECG is used to monitor left ventricular (LV) ischaemia during coronary angioplasty and to determine the duration of balloon inflation. Thirty patients undergoing elective single vessel angioplasty were studied by intravenous digital subtraction ventriculography, with 12 lead ECG being recorded throughout the procedure. Left ventriculograms were acquired in 10 patients after 20 s (group 1) and in 20 patients after 60 s (group 2) of the third balloon inflation. They were also acquired before and after the procedure. Compared with pre-angioplasty values LV ejection fraction (EF) fell during balloon inflation in all patients (mean 69% to 51%, $p < 0.001$) while only 21 patients developed ST segment elevation. Twenty three patients developed a new wall motion abnormality—all in left ventricular segments subtended by the treated artery. Only 16 of these, however, demonstrated coexistent ST segment elevation in leads that also corresponded to ischaemic segments. There were no differences between group 1 and group 2 in terms of the reduction in mean LVEF (68% to 48% *vs* 69% to 53% respectively) or the incidence of wall motion abnormalities (6/10 *vs* 17/20 respectively).

Balloon inflation during coronary angioplasty induces profound abnormalities of global and regional left ventricular performance, the degree of these is not lessened by shorter inflations, and the abnormalities may not be detected by ECG monitoring.

Intravenous digital subtraction aortography in acute aortic dissection

J Lyons, A Gershlick, M Norell, C Layton
The London Chest Hospital, London

Conventional investigation of aortic dissection involves direct cineaortography or computed tomography where available. We have evaluated intravenous digital subtraction aortography in 11 patients presenting with suspected acute aortic dissection. Digital aortography was performed as the initial investigation in nine cases. In five of these dissection of the ascending aorta was demonstrated and surgical repair was undertaken without further investigation. Additional cineaortography in the other four patients confirmed the digital aortography findings of an aortic dissection confined to the descending aorta in one case and no dissection in three. In two of the 11 patients cineaortography was performed as the initial investigation. The results of subsequent digital aortography concurred with those of cineaortography in both cases, dissection of the ascending aorta being shown in one. In two cases in which cineaortography and digital subtraction aortography were both normal, computed tomography showed evidence of a possible healed dissection. Thus surgery was not necessary

Digital subtraction aortography is a valuable technique for diagnosing acute aortic dissection, with no false positive or false negative findings when compared with cineaortography. Since it is a less traumatic procedure than direct cineaortography it should be the investigation of choice if computed tomography is not immediately available.

Myocardial perfusion imaging with contrast echocardiography

B Griffin, A D Timmis, E Sowton
Guy's Hospital, London

Contrast perfusion echocardiography with 2 ml of hand agitated Urograffin (50% solution) was performed without complication in 27 patients with coronary artery disease. Twenty patients (group 1) were studied during routine coronary angiography in order to evaluate the potential of this new technique for defining regional perfusion in the human heart. Group 2 consisted of seven patients undergoing percutaneous transluminal coronary angioplasty (PTCA) of proximal lesions. Lesions in each of the three major coronary arteries (left anterior descending (LAD), right coronary artery (RCA), and circumflex (Cx)) were dilated in this group. In group 1 contrast enhancement occurred in every case in the expected distribution of the artery injected. In four patients contrast enhancement occurred in areas remote from the vessel injected because of a well established collateral supply (demonstrated by angiography). The contrast effect persisted for 71 (26) (SD) s. A repeat injection in six patients confirmed the reproducibility of the technique. In group 2 echocontrast was injected into the central lumen of the balloon catheter immediately before inflation. In each case regional enhancement of the myocardium was demonstrated. After balloon inflation the contrast enhanced area defined the area of dyskinesis.

These data indicate that contrast perfusion echocardiography can be performed safely and reproducibly in man and that selective intracoronary injection of echocontrast defines the perfusion territory of the vessel injected.

Is the thallium defect the most ischaemic region of the ventricle?

Ann Tweddel, W Martin, I McGhie, I Hutton
University Department of Medical Cardiology, Royal Infirmary, Glasgow

Myocardial flow was determined in the areas of thallium perfusion defects in 12 male patients at time of angiography. 60 MBq of thallium-201 was injected into the aortic root during the last 15 s of maximal symptom limited supine exercise. Myocardial flow was measured at rest before and immediately after exercise by means of xenon-133 myocardial clearance with direct intracoronary injection. Thallium defects were seen in 17 of 36 areas with supply attributable to each of the major vessels. In the region supplied by the left anterior descending coronary artery with no thallium defects mean flow at rest was 73 (12) ml/100 g/min, falling on exercise to 52 (12) ml/100 g/min. Where there was a thallium defect mean flow was 38 (5), increasing on exercise to 62 (7) ml/100 g/min. In regions supplied by the circumflex coronary artery, flow at rest was 56 (9) where a thallium defect was present and 59 (8) ml/100 g/min where it was not; flow increased to 79 (18) and 69 (6) ml/100 g/min respectively with exercise. Flows in the distribution area of the right coronary artery were similar whether or not a defect was present (43 (12) and 47 (11) at rest, and 48 (15) and 48 (14) ml/100 g/min on exercise). In five of 12 patients flow was greatest in the area of the thallium defect.

These results suggest that a perfusion defect on thallium scan does not necessarily indicate the region of the left ventricle in which the measured flow is most reduced, nor does it reflect a region in which flow is unable to respond to stress.

A bedside nuclear probe for detection and quantification of left to right intracardiac shunts

B A Gould, J R Turner, D H Keeling, N J Ring, A J Marshall
Departments of Cardiology, Radiology, and Nuclear Medicine, Greenbank and Derriford Hospitals, Plymouth

A rapid bedside technique for the demonstration of left to right intracardiac shunts and their accurate quantitation would have an important application in clinical cardiological practice. We have compared a cadmium telluride nuclear probe with an Elscint gammacamera in 31 patients 11 of whom underwent right heart catheterisation and oximetric measurement of the shunt. The nuclear technique consists of a rapid injection of 740 MBq (20 mCi) of technetium-99 m into the right antecubital vein and measurement of the pulmonary to systemic flow ratio (QP:QS) by the gamma variate technique. Data were not obtained in four patients because of fractionation of the injection in two and equipment faults in two. The mean (SD) difference between the size of the shunts measured by the nuclear probe and by the oximetric technique was 0·47 (0·82) and between the nuclear probe and the gammacamera it was 0·1 (0·71). Analysis of scatter plots showed a larger discrepancy with increased shunt size. For 22 of the 27 data sets there was complete agreement between the nuclear probe and gammacamera on the significance of the size of the shunt. Where differences did occur they were very small.

These data indicate that left to right intracardiac shunts can be measured accurately at the bedside in either the coronary care unit when rupture of the interventricular septum is suspected or in the outpatient department.

Intravenous and intra-arterial digital subtraction arteriography compared in coronary bypass patients

H O'Kane, A McNeill, E McIlrath, J Cleland
Cardiac Surgical Unit, Royal Victoria Hospital, Belfast

Digital subtraction arteriography (DSA) offers a quick and low risk method of visualising coronary bypass grafts. The effectiveness of intravenous and intra-arterial DSA in visualising internal mammary artery (IMA) and vein grafts was compared in 35 patients eight to twelve days after operation. All patients had either one or two IMA grafts and 32 also had vein grafts. Both intravenous and intra-arterial DSA were carried out in all patients. A size 5 French gauge catheter was advanced centrally to the right atrium (intravenous DSA) or aortic root (intra-arterial DSA) from a peripheral vein or femoral artery respectively. The patients were not sedated nor were any of their drugs (such as dipyridamole/aspirin) stopped for the study. In the intravenous investigation 40 ml of Iopamidol (20 ml/s) was injected and for the intra-arterial investigation 20 ml of Iopamidol (10 ml/s) was used. There were no complications and specifically there were no femoral artery problems. Graft visualisation was scored from 0 to 3 (non-visualisation to excellent visualisation) and each graft was divided into a proximal and distal segment. Intra-arterial DSA visualised 98% of IMAs compared with 75% by intravenous DSA; 77% of vein grafts were visualised by intra-arterial DSA and 66% by intravenous DSA. Intra-arterial DSA is better than intravenous DSA for coronary bypass revisualisation. It would be of clinical value only in IMA but not vein graft revisualisation.

Exercise digital cardiac fluoroscopy: a new non-invasive technique for the identification of severe coronary disease

J Lyons, M Norell, J Gardener, R Balcon, C Layton
The London Chest Hospital, London

Digital angiographic systems can detect minor changes in *x* ray attenuation. Changes in heart volume during the cardiac cycle can therefore be detected without the use of contrast medium. Phase/amplitude analysis can be used to produce images of the timing and amplitude of such changes. We have named this technique digital cardiac fluoroscopy (DCF). To assess DCF in the detection of left ventricular wall motion abnormalities we studied 20 patients shown angiographically to have coronary artery disease (CAD). All patients underwent DCF at rest and 11 were also examined at peak exercise. Images were acquired in the right anterior oblique projection at 12·5 frames/s and phase/amplitude analysis was performed over three cardiac cycles. Cine left ventriculograms (CLV) and DCF were reported in random order after division of the ventricle into three segments. Resting DCF detected wall motion abnormalities appropriate to the CAD in 16 cases, including two with a normal CLV. The DCF was normal in four cases despite an abnormal CLV in three. There was a deterioration in wall motion in eight of the 11 patients undergoing exercise DCF. This group contained all patients with two and three vessel disease. There was either no change or an apparent improvement in wall motion in the remaining three patients, all with one vessel disease.

Exercise DCF is a new non-invasive method of detecting left ventricular wall motion abnormalities, which potentially can discriminate between minor and severe CAD.

The internal mammary artery: the graft of choice

H O'Kane, I Galvin, D J Gladstone, J Cleland
Cardiac Surgical Unit, Royal Victoria Hospital, Belfast

Significantly better graft patency, long term patient survival, and reoperation free survival are all associated with the internal mammary artery (IMA) graft. For these reasons we returned to using the IMA and have studied 279 patients who have received 367 IMA grafts since October 1984. Serial cardioselective enzymes (CK MB) and ECGs were recorded after operation in all patients and digital subtraction arteriography (DSA) was done in 87% of patients before hospital discharge. The only contraindication to the use of the IMA was emergency operation for failed angioplasty. The patients were aged up to 70 years, with the usual sex ratio, and their left ventricular function ranged from 17% to 70%. There were 194 patients with a single IMA and 86 patients with double IMAs, these included patients who had sequential and free IMA grafts. Apart from 34 patients who received an IMA graft only, all the others also received vein grafts (1–5). Other procedures carried out included valve replacements (5 mitral, 2 aortic) and closure of an atrial septal defect. A comparable group of 125 patients with vein grafts alone, operated on over the same period, were also followed up but they did not have DSA. There was no significant difference between the perioperative infarction rates (6·5% IMA, 7·5% vein graft) or the mortality rates (2·8% IMA, 1·6% vein graft). Digital subtraction arteriography showed that 96% of IMAs studied were patent at hospital discharge.

This experience confirms the IMA as our graft of choice in all cases requiring elective revascularisation and encourages us to expand its use.

Assessment of coronary artery bypass graft flow by intraoperative Doppler ultrasound

I A Simpson, T J Spyt, D J Wheatley, S M Cobbe
University Departments of Medical Cardiology and Cardiac Surgery, Royal Infirmary, Glasgow

Measurement of coronary artery bypass graft flow by an electromagnetic flowmeter has several disadvantages, in particular the need for satisfactory circumferential electrical contact. Doppler ultrasound has been successfully used to measure aortic blood flow non-invasively and has the potential to assess flow in coronary artery grafts intraoperatively. We have studied 20 grafts in 10 patients aged 31–67 years (mean 55 years) undergoing coronary bypass surgery. After termination of cardiopulmonary bypass intraoperative Doppler ultrasound examination was performed by means of a 10 MHz pulsed Doppler pencil probe and a Vingmed Alfred Doppler velocimeter interfaced to a spectrum analyser. The probe was positioned directly on the coronary graft and angulation to blood flow was minimised. Mean graft flow velocity was calculated by a frequency follower and vessel diameter by direct callipers measurement. Electromagnetic flowmeter recordings were performed for comparison. Doppler derived flows ranged from 0 to 160 ml/min (mean 89·5 ml/min) and compared well with those obtained by electromagnetic flowmeter recordings (0 to 120 ml/min (mean 65·3)) ($r = 0{\cdot}77$).

Doppler ultrasound provides a satisfactory method of assessing coronary artery bypass graft flow intraoperatively; it may also prove suitable for measuring flow in native coronary vessels.

Assessment of myocardial revascularisation at the time of graft completion by monophasic action potential recordings

P Taggart, P Sutton, M Runnalls, W O'Brien, R Donaldson, R Hayward, H Swanton, R Emanuel, T Treasure

Departments of Cardiology, Physiology, Cardiothoracic Surgery, and Anaesthesia, The Middlesex Hospital and Medical School, London

Observations in animals and during cardiac catheterisation in man have shown that monophasic action potential (MAP) recordings provide a highly sensitive measure of localised myocardial ischaemia. We have developed an electrode suitable for recording from the epicardium during coronary artery bypass surgery. A bipopular pressure contact silver/silver chloride electrode is secured in an acrylic mount that is grooved to allow it to be held between the index and middle fingers. The design enables it to be slid within the pericardium between the rib cage and left ventricular free wall and positioned at any selected recording site with minimal displacement of the heart. We have tested the ability of the electrode to quantify short periods of local ischaemia in eight patients undergoing routine coronary artery bypass surgery (4 left internal mammary anastomoses (LIMA) and a total of 27 saphenous vein grafts (SVG)). After completion of all grafts blood flow to the myocardium was reduced for 90 seconds by means of different permutations of SVG and LIMA occlusion. In all patients the MAP demonstrated typical ischaemic changes (for example loss of amplitude 33·3 (4·3) mV to 25·7 (4·2) ($p < 0·005$), loss of diastolic potential 21·1 (2·9) mV to 17·1 (2·9) ($p < 0·005$), and shortened duration at 90% repolarisation 286·0 (20·7) ms to 261 0 (15·2) ($p < 0·001$)).

Our results so far indicate that: *(a)* the electrode design is capable of providing stable MAP signals from any selected area of the left ventricular epicardium; *(b)* the MAP recordings provide a useful quantitative index of ischaemia; *(c)* the high sensitivity of the technique enables results to be obtained with relatively short periods of interruption of blood flow and this makes the method quick, simple, and without hazard to the patients; *(d)* the technique is applicable to assessing regional ischaemia, the viability of specific areas of myocardium, and the efficacy of individual grafts.

The assessment of coronary artery bypass grafts by magnetic resonance imaging with velocity mapping

S R Underwood, D N Firmin, R H Klipstein, R S O Rees, D B Longmore
Magnetic Resonance Unit, National Heart and Chest Hospital, London

Flowing blood usually gives no magnetic resonance signal and patent coronary artery grafts should be identified by this contrast with surrounding structures. This study tests this assumption and explores the additional information provided by magnetic resonance velocity mapping. Ten patients with a total of 36 grafts were studied. Diastolic images were acquired in transverse, sagittal, and oblique planes through the ascending aorta, and the grafts were considered to be patent if they could be identified and followed for most of their length. Velocity mapping was performed by a cine field echo sequence and measurements were made throughout diastole. Angiography showed 27 grafts to be patent, and in 23 the results of conventional magnetic resonance imaging accorded (sensitivity 85%). No occluded grafts were incorrectly assigned by magnetic resonance (specificity 100%). Of the four patent grafts that were not detected, two were small and served diseased vessels with poor run off. Velocity mapping was performed in eight patients and measurements were obtained in six of them. Peak velocities in the grafts in early systole ranged from 74 to 640 mm/s. An independent assessment of graft function was not available, but in one patient in a graft with good run off, velocity was high (326 mm/s peak), and in a graft with poor run off it was low (74 mm/s peak).

Conventional magnetic resonance imaging is sensitive and specific in the detection of patent coronary artery bypass grafts. Velocity mapping did not improve sensitivity, but it did provide a measure of graft function.

Secretion of human atrial natriuretic peptide from the heart

D R J Singer, J W Dean, M Buckley, G A MacGregor
Blood Pressure Unit, Department of Medicine and Department of Physiology, Charing Cross and Westminster Medical School, London

Atrial natriuretic peptides (ANP) have recently been isolated and synthesised from mammalian heart. A growing body of evidence suggests that increased atrial pressures are a mechanism for release of ANP. Studies directly exploring cardiac release of ANP, however, have been confined to groups of patients in whom atrial pressure is abnormally high. We therefore studied eight patients undergoing elective cardiac catheterisation and angiography who had no overt clinical features of cardiac failure. All had normal renal and liver function and normal resting cardiac pressures. ANP was measured by radioimmunoassay after extraction. Plasma ANP concentration was significantly higher in the right atrium (45·2 (8·6) pg/ml; p < 0·05), right ventricle (43·8 (7 7) pg/ml), and pulmonary artery (43·1 (6 8) pg/ml; p < 0·01) than in the superior vena cava (32·0 (5 4) pg/ml). In three of the eight subjects there was no increase in the release of ANP into the right atrium. There was, however, a consistent rise from the superior vena cava to right ventricle for all eight subjects. We attribute this to incomplete atrial mixing of blood because of streaming and the high local concentration of ANP in blood leaving the coronary sinus. In contrast with the increase in concentrations across the right side of the heart, there was no significant difference in plasma ANP between the right heart and left ventricle (38·2 (4·5) pg/ml). The increase in plasma ANP of 11·8 pg/ml from the superior vena cava to the right ventricle indicated that the mean right atrial secretion rate for these subjects was approximately 940 pg/s. The ANP increase across the heart from superior vena cava to the left ventricle was, however, only 6·1 pg/ml, giving a lower net cardiac secretion rate of approximately 500 pg/s.

There is increasing evidence that ANP is important in the pathophysiology of many disorders of sodium and water balance. These studies clearly demonstrate that the heart secretes atrial natriuretic peptides into the right atrium in the presence of normal cardiac pressures.

Mechanisms underlying polyuria accompanying supraventricular tachycardia in man

G C Kaye, P Baylis, P J Lowry, A J Camm
St Bartholomew's Hospital, London

Changes in urine flow, free water and sodium excretion, plasma catecholamines, renin arginine-vasopressin (AVP), and atrial natriuretic peptide (ANP) were studied in ten patients (five men) with induced supraventricular tachycardia (SVT). Five patients were water loaded (group 1) to determine changes in urine flow and composition and five patients were not water loaded (group 2) to determined the role of AVP. The arrhythmia was initiated and terminated by programmed stimulation from the atria (9 cases) or from the ventricle (1 case). This was done at a similar time of day for each patient and for group 1 during constant urine flow. Group 1 patients were aged 21–72 (mean 48) years and group 2 were 42–58 (mean 48) years. One patient in group 2 had clinical polyuria. The duration of tachycardia in group 1 was 29 min and in group 2 it was 34 min; heart rates were 184 (18) and 181 (27) beats/min respectively (NS). In group 1 urine flow increased from 5·1 (1·0) ml/min immediately before tachycardia initiation to 10·4 (1·9) ml/min (p < 0·001) immediately after the end of tachycardia and in group 2 it increased from 2·4 (1·2) ml/min to 5·2 (1 6) ml/min (p < 0·05). There was a significant increase in both free water (p < 0·001) and sodium excretion (p < 0·05) in both groups. During the arrhythmia there was no discernible pattern in plasma catecholamines and renin and plasma AVP was unchanged. In two patients in group 2, one with polyuria, there was a significant rise in plasma ANP during the arrhythmia, but ANP increased by a similar amount in a group of patients without such polyuria.

Changes in plasma AVP do not account for the increase in free water excretion during induced SVT. Changes in plasma ANP do not account for the polyuria, and this suggests that an additional diuretic factor is responsible for the increase in free water excretion.

Rapid atrial pacing releases atrial natriuretic peptide, suppresses renin secretion, and causes diuresis

K P Walsh, T D M Williams, R Canepa-Anson,
E Pitts, S L Lightman, R Sutton
Westminster Hospital, London

Paroxysmal tachycardias (PT) are often accompanied by polyuria. Plasma concentrations of atrial natriuretic peptide (ANP) have recently been found to be increased during PT. We present an animal model for PT and its associated haemodynamic, renal, and neuroendocrine changes. Seven male greyhounds anaesthetised with chloralose were paced from the right atrial appendage for one hour at 250 pulses/min. Haemodynamic measurements, arterial plasma samples (ART), and urine collections were taken every 30 min for 90 min before and after rapid atrial pacing. In addition, blood was sampled from the proximal coronary sinus (CS) for the estimation of ANP concentrations. Rapid atrial pacing produced a pronounced rise of mean pulmonary wedge pressure (from 2·4(0·9) to 8·0(1·5) mm Hg, mean (SEM), p<0·01) accompanied by small decreases in cardiac output (from 4·69(0·33) to 3·75(0·26) l/min, p<0·01) and in mean arterial pressure (from 151(6) to 139(5) mm Hg, p<0·01). Plasma renin activity decreased during pacing from 5590(1300) to 2660(330) ng AI/h/l (p<0·05) and there was a rebound increase to 8230(1330) ngAI/h/l 60 min after pacing. Coronary sinus ANP concentrations were initially sevenfold greater than arterial concentrations and both increased during pacing (ANP_{cs} 86(12) to 515(63); ANP_{art} 12(3) to 146(41) pmol/l (p<0·05). Urine flow increased from 3·2(0·6) to 5·5(0·5) ml/min (p<0·05) during the latter 30 min of rapid pacing.

Rapid atrial pacing causes a pronounced rise in left atrial pressure accompanied by a considerable release of ANP from the coronary sinus and an increase of arterial ANP concentrations. This is followed by diuresis and suppression of renin secretion.

Effect of calcitonin gene related peptide on haemodynamic function and regional blood flow in experimental chronic heart failure

I S Anand, J Gurden, P A Poole-Wilson, P Harris
The Cardiothoracic Institute, London

Human calcitonin gene related peptide (hCGRP) is a recently discovered regulatory peptide with widespread distribution that includes the atria, cardiac nerve fibres, and blood vessels. hCGRP circulates in normal subjects and is one of the most potent endogenous vasodilators in man. In view of the possible role of hCGRP in controlling peripheral vascular tone, we studied the effects of hCGRP infusion on the haemodynamic function and regional blood flow in a group of five normal rabbits and in a group of five rabbits with doxorubicin induced cardiomyopathy in heart failure. Two days before the study catheters were implanted into the right atrium, left ventricle, and ascending aorta. A specially designed thermistor catheter was inserted into the descending aorta. Studies were made on conscious animals at rest. Cardiac output was measured by thermodilution and regional blood flow by radioactive microspheres. In the normal rabbits hCGRP reduced the mean systemic pressure from 90(17) to 61(7) mm Hg (mean (1 SD), p<0·01), increased cardiac output from 342(96) to 449 (137) ml/min/kg (p<0·05), and increased heart rate from 274(21) to 321(20) beats/min (p<0·05). There was a significant increase in renal and myocardial blood flow (p<0·05). hCGRP had similar effects in the cardiomyopathic rabbits. Mean systemic pressure fell from 96(15) to 63(16) mm Hg (p<0·01), cardiac output increased from 230(44) to 287(17) min/ml/kg (p<0·05), and heart rate increased from 286(17) to 315(21) beats/min. Renal and myocardial blood flow also increased (p<0·05).

These data confirm that hCGRP is a powerful vasodilator, but they show that the increase in blood flow is limited to renal and myocardial tissues.

One thousand heart attacks in Grampian: the place of cardiopulmonary resuscitation in general practice

J M Rawles, G R Pai, Neva Haites
Department of Medicine, University of Aberdeen, Aberdeen

We report the outcome of 1011 heart attacks that occurred in patients under the care of general practitioners who practised cardiopulmonary resuscitation and were equipped with defibrillators. The incidence of heart attacks was 3·5 per thousand population per year; the 28 day mortality was 36%, and 17% died before being seen by a doctor. The general practitioner was the first medical contact in 92% of heart attacks, and in 80% of such calls he had a defibrillator with him. Fifty six patients had cardiac arrest in the presence of a general practitioner and resuscitation was attempted in 47 cases, representing 5% of all heart calls. Twenty one (45%) resuscitated patients reached hospital alive and 13 (28%) survived to leave hospital.

The opportunities for cardiopulmonary resuscitation in general practice are sufficiently frequent to warrant the training and equipping of general practitioners for advanced life support. The results of resuscitation by general practitioners working alone compared favourably with those of hospital based mobile coronary care units.

The inability of trained nurses to perform basic life support: failure of a critical link

Geralyn Wynne, Theresa Marteau, Marie Johnson, T R Evans, Carolyn Whiteley
The Royal Free Hospital and School of Medicine, London

A large proportion of cardiac arrests in hospital occur on the ward. Prompt and effective basic life support (BLS) increases survival after cardiac arrest and thus BLS must be started by the nursing staff. The first aim of this study was to assess the effectiveness of BLS skills in trained nurses and the second aim was to examine the relation between nurses' perceived skills and their actual skills. The sample comprised 53 trained nurses attending an orientation course at a London teaching hospital who were tested without prior warning. Skills were assessed on a recording manikin. Experience of BLS, self reported confidence, and beliefs about the effectiveness of BLS were assessed by a questionnaire. Twenty two nurses completed the BLS assessment before completing the questionnaire, while the remainder completed the questionnaire first. None of the nuses performed BLS adequately by national standards; 57% were assessed as being completely ineffective. Experience was related to confidence but not to competence at performing BLS. Sisters were significantly more confident than staff nurses (F = 3·75; $p < 0·05$) but no more competent. Nurses scoring higher on BLS skills assessment estimated the procedure as being significantly more successful than those with lower scores (t = 2·36; $p < 0·05$). Nurses who completed the self ratings after completing the BLS assessment gave significantly lower estimates of their skills than those completing the ratings first (t = 2·20; $p < 0·05$).

The results show that the BLS skills of trained nurses are as poor as those reported for doctors. BLS by nurses is an essential part of ward resuscitation and ways of improving nurse training will be discussed.

Physical rehabilitation of coronary patients in the community

H J N Bethell
Basingstoke District Hospital, Basingstoke, Hampshire

A controlled trial of exercise training for patients recovering from acute myocardial infarction is reported. Two hundred consecutive patients treated in a district general hospital coronary care unit were randomised to either a three month course of physical training or a control group. 82% of the treated patients finished the course, which was held in a local sports centre. The physical fitness of the treatment group, as measured by the predicted maximum oxygen uptake, increased by 27% compared with 14% for the controls ($p < 0·001$). The myocardial work at a submaximal exercise load as measured by the double product fell by 12·8% in the treatment group and by 0·6% in the controls ($p < 0·001$). The prevalence of angina fell by 10% in the treatment group but rose by 60% in the controls. The energy level in the treatment group rose by 36% more than it did in the controls.

The use of community sports facilities to rehabilitate coronary patients is effective and cheap and could meet a need which is not catered for by most hospitals in the United Kingdom. Conducting the exercise course away from the hospital makes it less like treatment and more like fun, thus encouraging compliance.

Management of myocardial infarction in Scotland

S J Hutchison, S M Cobbe
University Department of Medical Cardiology, Royal Infirmary, Glasgow

A questionnaire on the management of myocardial infarction was sent to 160 consultants in Scotland; 120 (80%) replied. Sixty nine (54%) of respondents were based in teaching hospitals and 54 (28%) were cardiologists or physicians with an interest in cardiology. Forty two (38%) were participating in studies of early management, primarily of thrombolytic treatment. Three (2·3%) used β blockers routinely in the acute phase. Significantly more physicians than cardiologists treated "warning" arrhythmias with lignocaine (65 (70%) *vs* 13 (37%), $p < 0\ 01$). Physicians and cardiologists differed in their use of β blockers (29 (31%) *vs* 21 (58%), $p < 0·01$) and of exercise testing (23 (25%) *vs* 23 (64%), $p < 0·01$) in long term management). Fifty two (56·5%) of physicians did not use β blockade nor did they perform exercise testing for risk stratification after infarction (8 (22·2%) of cardiologists, $p < 0·01$).

These results suggest that cardiologists have been more influenced by recent studies of postinfarct management than have general physicians, either in prescribing β blockers or attempting to identify high risk cases by exercise testing.

Is there a correlation between exercise tolerance and haemodynamic variables in patients with chronic severe left ventricular dysfunction?

A O Molajo, D H Bennett, C Ashcroft, S B Lucas
Regional Cardiac Centre, Wythenshawe Hospital, Manchester

Current practice in the evaluation of drugs for the treatment of patients with chronic left ventricular dysfunction (CLVD) involves the assessment of the effect of the drugs on resting haemodynamic variables. Frequently a favourable haemodynamic response is not associated with improvement in exercise tolerance. In order to explain this discrepancy we investigated the relation between the resting haemodynamic variables and exercise tolerance in 26 patients with dyspnoea of effort secondary to left ventricular (LV) dysfunction. Treadmill exercise tolerance testing was performed within 48 hours of the haemodynamic assessment, without change in their treatment and by means of the most suitable predetermined patient matched protocol. The mean angiographically determined left ventricular ejection fraction was 39 (21%) (mean (SD)). Exercise tolerance (202·5 (141·5%) × 10^3 J (range 30–644 × 10^3)) correlated significantly with resting mean pulmonary capillary wedge pressure (PCWP) (r= −0 74; p=0·007). There was no correlation between the exercise tolerance and stroke index, left ventricular end diastolic volume index, left ventricular end systolic volume index, stroke work index, systemic vascular resistance, pulmonary vascular resistance, or LV ejection fraction.

These findings indicate that in CLVD patients resting PCWP is a major indicator of exercise tolerance but other indices of left ventricular function are not. This may partially explain the discrepancy between drug effect on haemodynamic variables and exercise capacity.

Nitrate tolerance: prevention by intermittent dosing

J C Cowan, J P Bourke, D S Reid, D G Julian
Department of Cardiology, Freeman Hospital, Newcastle upon Tyne

Sustained exposure to nitrates may increase susceptibility to tolerance. An investigation was undertaken to compare the extent of the development of tolerance during continuous and intermittent treatment with glyceryl trinitrate patches. The study was divided into short term and long term phases, each with a double blind crossover design. Exercise testing was performed before and 3·5 hours after application of an active (10 mg Transiderm) or placebo patch (short term). The long term phase consisted of two one week treatment periods with crossover between continuous active and intermittent active treatment. Patches were changed twice daily at 8 am and 8 pm (continuous treatment, 8 am active and 8 pm active; intermittent treatment, 8 am active and 8 pm placebo). Exercise testing was performed on day 8 of each treatment period with the previous evening's patch still in position and repeated 3·5 hours after active patch application. Twelve patients were studied. Short term active treatment prolonged mean (SEM) exercise time (active 428 (30) s; placebo 361 (26), p<0·01). In the long term phase, this benefit disappeared during continuous treatment (continuous active 363 (23) s; placebo period of intermittent treatment, 348 (30), p>0·05). By contrast, the benefit was fully maintained during intermittent treatment (continuous active 370 (21) s; active period of intermittent treatment 432 (21), p = 0·01).

It is concluded that complete tolerance develops during continuous treatment with glyceryl trinitrate patches but that antianginal efficacy is fully maintained when patches are removed for 12 hours overnight. This result suggests that constant exposure to nitrate increases susceptibility to tolerance.

Differential contributions of the coronary arteries to left ventricular flow during stress

Ann C Tweddel, W Martin, I McGhie, I Hutton
University Department of Medical Cardiology, Royal Infirmary, Glasgow

The contributions from each major coronary vessel to total left ventricular flow during stress were determined in nine patients with arteriographically normal coronary vessels and right dominant systems. Myocardial flow was measured by clearance of xenon-133 injected into each of the major coronary vessels. Measurements were made at rest, during atrial pacing at 90 and 110 beats/min, and immediately after maximal supine exercise. Total left ventricular flow increased with atrial pacing at 90 beats/min by 14·3 (1)% (p<0·02) and at 110 beats/min by 45·8 (16) (p < 0·02) and immediately after exercise by 18·5 (5)% (p<0 05). In the area of distribution of the left anterior descending artery, flow increased by 13 (2)% (p<0·02) with atrial pacing at 90 beats/min and by 40 (1)% (p<0 02) with atrial pacing at 110 beats/min and by 18 (7)% (p<0·02) immediately after exercise. In the area of distribution of the circumflex artery, flow increased by 16 (3·6)% (p<0·02) with atrial pacing at 90 beats/min, by 51 (14·6)% (p<0·02) with pacing at 110 beats/min, and by 24 (6)% (p<0·02) immediately after exercise. In the inferior surface of the left ventricle, supplied by the right coronary artery, flow was unchanged with atrial pacing at 90 beats/min (−3·6% (1)%), atrial pacing at 110 beats/min (−0·4 (2)%), or after exercise. Maximal variation in area of distribution was ±8% and was unchanged by atrial pacing or after exercise.

In conclusion, increased myocardial flow in response to stress is provided by the left coronary artery, with little change in the right coronary artery flow. This suggests a mechanism for the differing impacts of anterior and inferior ischaemia and infarction on left ventricular dysfunction.

A clinical profile of 200 patients with palpitation

C P Lau, G C Kaye, J Elbstob, D Mehta, A J Camm
Department of Cardiology, St Bartholomew's Hospital, London

Questionnaires were completed by 200 consecutive patients who had presented with palpitation to the department of cardiology over an 18 month period. There were 102 men (aged 18–72 years) and 98 women (aged 18–76 years). 95% presented within one year of the onset of symptoms. 41% had supraventricular reentrant tachycardia (SVT) of whom 63% had Wolff-Parkinson-White (WPW) syndrome and 26% had intranodal tachycardia, 22% had atrial fibrillation, 5% had atrial flutter, 4% had automatic atrial tachycardia (AAT), 14% had ventricular tachycardia, and 6% had atrial or ventricular extrasystoles. Palpitation lasted for minutes (53%), hours (50%), or days (15%). Nine (5%) patients had continuous palpitation; most of them were having AAT. Other symptoms during palpitation included dyspnoea (60%), dizziness (56%), and chest pain (50%). 26% of all patients had at least one episode of syncope and 35% of these had frequent blackouts despite regular treatment. 20% of patients passed much more urine than normal during palpitation and there was a strong association with SVT, particularly WPW (58%) and atrial fibrillation (20%). 43% of this group of patients found this effect inconvenient. At the time of presentation, 26% were taking β blockers, 33% were on other antiarrhythmics, and 54% were on combination treatment. Despite regular medication 36% continued to have palpitation lasting for hours and 18% had daily attacks. Of the six patients who had operation, one still had daily palpitation, four were on medication, one had a pacemaker, and only one was on no other treatment. Only 10 of the 16 patients treated by pacing were on no other treatment.

In conclusion, patients with paroxysmal arrhythmias continue to have frequent and disabling symptoms despite treatment.

Is single coronary artery occlusion in young adults the result of abnormal platelet function?

A H Gershlick, Denise Syndercombe Court, P G Mills, R Balcon
The London Chest Hospital and The London Hospital, London

In young patients who suffer myocardial infarction a single coronary occlusion is often demonstrated. Frequently the remaining arteries are angiographically normal. To determine whether occlusion could be due to spontaneous thrombus formation or an abnormal thrombotic reaction to minor atheromatous plaque trauma we have studied three groups each of 25 male patients: group I (<45y) with single coronary occlusion; group II (<45y) symptom free controls; and group III (>50y) with known multivessel disease. In these groups platelet aggregometry was used to determine the platelet activation index (a measure of platelet hyperactivity). We measured concentrations of platelet factor 4 and β thromboglobulin (βTG) to evaluate platelet release reaction and fibrinogen, antithrombin III, and α^2 antiplasmin to assess thrombotic tendency. Smoking habit, family history, and lipid status were documented. Cigarette smoking was more common in group I patients than in group II (15/25 *vs* 3/25, $p<0{\cdot}01$). The platelet activation index was also significantly greater in group I than in group II (mean (SD), 4·25 (2·19) *vs* 3·26 (0·96), $p<0{\cdot}02$), indicating that group I patients had hyperactive platelets. No significant increase in platelet activation index was found in patients with multivessel disease (group III). While mean (SD) concentrations of fibrinogen and βTG in group III were significantly greater than in group II (fibrinogen 2·50 (0·26) *vs* 2·25 (0·27) g/l, $p<0{\cdot}005$; βTG 66·73 (62·2) *vs* 36·4 (14·03) ng/ml, $p<0{\cdot}05$), this is likely to be secondary to their atheroma. No such increases were seen in group I. Since smoking was more common in group I this may have exacerbated their underlying platelet abnormality. Such platelet hyperactivity may be the primary cause of coronary occlusion in young patients.

Thombolytic treatment in acute myocardial infarction complicated by cardiogenic shock

M P S Varma, T McLean, E Chadwick, D Anderson, K Hicks
Cardiac Unit, Erne Hospital, Enniskillen, County Fermanagh, Northern Ireland

Fifteen patients aged between 40 and 75 (mean 57·1 years) with acute myocardial infarction, complicated by cardiogenic shock (systolic blood pressure <80 mm Hg despite intervention) and who had had symptoms for less than six hours (mean 137 min) were given 1·5 million units of streptokinase intravenously over 30 min followed by full heparinisation. Nine (60%) patients had a previous history of angina or myocardial infarction. Eleven (73·3%) patients are alive and four (26·7%) patients died in hospital. Angiography was performed in eight patients within 10 days of streptokinase. None of the patients showed clinical evidence of reocclusion before angiography. Mean time to reperfusion as judged by ST segment regression, increase in blood pressure, and clinical criteria was 78·1 min. There was angiographic evidence of reperfusion in all eight patients. Reperfusion ventricular arrhythmias were seen in each successful case and, with the exception of ventricular tachycardia in one patient, the other arrhythmias were transient and did not require any intervention. Two patients had urgent bypass grafting and one had percutaneous transluminal angioplasty. The remaining patients were managed conservatively.

Cardiogenic shock has a very high mortality. Intravenous streptokinase may be used in this condition to open up infarct related arteries (in about 73% of patients in this series) thus preserving myocardium and improving morbidity and mortality.

Coronary occlusion in acute myocardial infarction is frequently intermittent

D Hackett, G Davies, S Chierchia, A Maseri
Royal Postgraduate Medical School, Hammersmith Hospital, London

Thrombolytic treatment has clearly established the importance of thrombosis in maintaining coronary occlusion in acute myocardial infarction (AMI), but the initiating mechanism is less clear. Holter monitoring was started immediately on presentation in 45 patients with AMI of less than four hours duration who had coronary arteriography (CA) and intracoronary streptokinase infusion. At CA 38 patients had total coronary occlusion and seven had subtotal coronary occlusion. Thrombolysis induced reperfusion in 37 (82%) patients 81–530 (mean 283) min after the onset of symptoms. Twelve episodes of intermittent resolution and re-evaluation of the ST segment were seen during Holter monitoring in 8 (18%) patients before CA was performed. Three similar episodes occurred before and 25 during continuous streptokinase infusion in 16 (36%) patients studied by CA, confirming that coronary reopening and reocclusion were associated with these episodes. When reocclusion was observed at CA, intracoronary isosorbide dinitrate 2 mg was followed up by reopening on 14 (50%) occasions in 11 (69%) patients. Holter recording in two patients in the 24 hours before AMI showed frequent transient episodes of ST segment elevation. In total, 50 episodes of coronary reocclusion were found in 22 (49%) patients. There was no difference in the severity of the mean (SD) residual minimal coronary stenosis diameter immediately after thrombolysis between those patients with (1·08 (0 4) mm and without (1·14 (0·3) ($p = 0·6$) reocclusion.

Intermittent coronary occlusion is found before, at the onset, and during the evolution of AMI and might explain the variable time course of its evolution. Coronary reocclusion responsive to nitrates during intracoronary thrombolytic treatment suggests that vasoconstriction may contribute to coronary occlusion in AMI.

Hypertensive left ventricular hypertrophy: identification of a high risk subgroup

S D Pringle, F G Dunn, J McKillop,
P W Macfarlane, A R Lorimer
University Departments of Medicine and Medical Cardiology, Royal Infirmary and Stobhill General Hospital, Glasgow

Hypertensive patients with electrocardiographic left ventricular hypertrophy and strain (ECG-LVH and strain) have a threshold increase in mortality. This increased risk is in excess of that due to the level of blood pressure alone. We have therefore studied two groups of *symptom free* hypertensive patients. Group I (16 patients) consisted of those with ECG-LVH and strain. Group II (23 patients) did not have this abnormality. Exercise ECG, 24 hour Holter monitoring, and stress thallium scintigraphy were performed in all patients off treatment, and coronary arteriography was undertaken in the high risk group I patients. Two patients (both group I) had episodes of non-sustained ventricular tachycardia on Holter monitoring. All group I patients had accentuation of resting ST-T wave abnormalities during exercise. Reversible thallium perfusion defects were present in 9/16 patients in group I but in only 3/23 patients in group II. Moreover, of these nine patients with perfusion abnormalities, six had significant coronary artery disease (5 triple vessel disease, 1 single vessel disease). The remaining 10 patients in group I had completely normal coronary arteriograms.

Thus the higher mortality in hypertensive patients with LVH and strain may be partly explained by covert coronary artery disease. We therefore feel that coronary arteriography should be considered in these patients especially if ECG-LVH and strain is associated with reversible thallium perfusion abnormalities.

Raised concentrations of plasma atrial natriuretic peptide in cardiac transplant recipients

D R J Singer, M G Buckley, G A MacGregor,
A Khaghani, N R Banner, M H Yacoub
Blood Pressure Unit, Department of Medicine,
Charing Cross and Westminster Medical School,
London; and Cardiac Unit, Harefield Hospital,
Harefield, Middlesex

There is increasing evidence that the atrial natriuretic peptides (ANP) are an important new hormonal system for the regulation of sodium and water balance. Raised concentrations have been demonstrated in cardiac failure and in some patients with high blood pressure. Mechanisms determining release of ANP are not fully understood, however, in particular whether atrial autonomic innervation has a role. In view of the denervation of the transplanted heart and the increased amount of atrial tissue present after transplantation we have measured plasma concentrations of ANP in cardiac transplant recipients. We studied eight white cardiac transplant recipients (6 male and 2 female, mean age 42 years, weight 67·5 (3·9) kg, average (SEM) supine blood pressure 135/90 (4·2/2·5) mm Hg) and eight control subjects matched for age, sex, race, and blood pressure (mean age 42 years, weight 79·4 (4·7) kg, mean supine blood pressure 140/90 (5·1/2·7) mm Hg) on their normal diet. The patients had no evidence of significant rejection on cardiac biopsy 6–77 weeks after transplant. In one venous pressure was slightly raised. None of the remaining seven had clinical features of cardiac failure. All had plasma creatinine $<162\,\mu$mol/l (123 (10) μmol/l). Treatment was by immunosuppression (cyclosporin and azathioprine) in eight, antiplatelet in seven (low dose aspirin seven with dipyridamole in five), and vasodilators in six (nifedipine or hydralazine). Blood was taken in the morning after the patients had sat for 10 minutes, and ANP was measured by immunoassay after extraction. Plasma ANP concentration, was significantly higher in cardiac transplant recipients (19·4 (3·9) pg/ml) than in controls (7·3 (1·2) pg/ml) ($p<0\,01$). The ANP concentration was not overtly related to treatment, arterial pressure, or cardiac or renal function.

The mechanisms contributing to the raised concentrations are not clear. These findings appear to indicate that the transplanted atria are secreting atrial natriuretic peptides and to show that in man factors other than atrial innervation are of major importance in modulating ANP secretion.

A comparison of the St Jude medical and the Carpentier-Edwards xenograft valves in the mitral area

J Cleland, D Gladstone, L Hamilton, H O'Kane
Cardiac Surgical Unit, Royal Victoria Hospital,
Belfast

Results are compared over a 6½ year period in patients having isolated mitral valve replacement with a St Jude medical prosthesis (SJM) or a Carpentier-Edwards xenograft (CEX). 94 patients (aged 29–71 years with 63 women and 31 men) had a CEX and 85 patients (aged 5–70 years with 66 females and 23 males) had a SJM. Although they were not randomly allocated, the groups had comparable surgical techniques and myocardial protection was constant throughout the period. The CEX was used more frequently early in the study and therefore the follow up is longer (CEX 301 patient years; SJM 207 patient years). The 30 day mortality was 4·2% in the CEX group and 7% in the SJM group and late mortality was 8·5% and 5·3% respectively. There were no reported cases of primary structural failure or significant haemolysis in either group. All patients in the SJM group and 80% in the CEX group were anticoagulated. Thromboembolic episodes occurred in eight CEX patients (total of 14 events, 5 major and 9 minor), a rate of 4·6 events/100 patient years. In the SJM group six patients experienced isolated events (1 valve thrombosis and 2 major and 3 minor events), a rate of 2·9 events/100 patient years. Reoperation for periprosthetic leak has been required by five patients (CEX 2, SJM 3), and whereas there were no cases of endocarditis in the SJM group, there were three (2 Q fever) in the CEX group, with one death. Thromboembolism resulted in two deaths in the CEX group but there were no deaths from this cause in the SJM group.

The results in the two groups were therefore similar, with comparable numbers of patients alive and event-free at six years. Because of the known long term failure rate of tissue valves and the high percentage of tissue valves requiring anticoagulation, our choice for mitral valve replacement is the St Jude medical valve.

Hypertension, hypertrophy, and complex ventricular arrhythmias

J M McLenachan, E Henderson, K I Morris,
C Isles, H J Dargie
Cardiac Department, Western Infirmary, Glasgow

Electrocardiographic left ventricular hypertrophy (LVH) is associated with a high incidence of sudden death from presumed cardiac arrhythmia. Increased ventricular ectopic activity has been demonstrated in hypertensive LVH but the prevalence of ventricular tachycardia, which is highly predictive of sudden death in other forms of cardiac hypertrophy, is not known. We investigated the frequency of complex ventricular arrhythmias by 48 hour ambulatory ECG monitoring in 100 hypertensive patients of whom 50 had ECG LVH and 50 did not. To exclude any effect of hypertension itself on arrhythmia frequency, the groups were matched for initial and achieved blood pressure levels as well as for age, sex, and smoking habit. In addition, left ventricular mass was estimated by echocardiography and serum potassium concentration was measured. Ventricular tachycardia (VT), defined as >3 complexes at a rate >120 beats/min, occurred in 14/50 (28%) of those with ECG LVH and 4/50 (8%) of those without ($p<0.05$). Voltage evidence of LVH, ECG ST-T abnormalities, and left ventricular mass >350 g were all significantly more common in those patients with VT. Indeed, 11 (58%) of 19 hypertensive patients with LVH and "strain" had at least one episode of VT. The occurrence of VT was not related to initial or achieved blood pressure levels nor to serum potassium.

Thus ventricular tachycardia occurs commonly in hypertensive left ventricular hypertrophy and may contribute to the high mortality; its frequency is not attributable to higher blood pressure levels nor to hypokalaemia but is related to the degree of cardiac hypertrophy.

The digoxin-amiodarone interaction

K C Robinson, S Walker, A Johnston, J P Mulrow, W J McKenna, D W Holt
Royal Postgraduate Medical School, Hammersmith Hospital, London

Amiodarone increases pre-dose plasma digoxin but its effect on the absorption profile of digoxin and the persistence of the interaction during long term treatment are not known. Amiodarone, 800 mg daily for 7 days, was given to 10 patients (6F/4M) aged 51–72 (mean 63) with poorly controlled atrial fibrillation despite therapeutic doses of digoxin. The blood concentration/time curve and urinary clearance of digoxin were studied before and after 7 days' amiodarone treatment. In six patients digoxin measurements were repeated after a further 5 weeks of 400 mg amiodarone daily. After amiodarone 800 mg daily peak plasma digoxin concentrations increased from 1·8 (0·8) to 3·2 (1·7) ng/ml ($p<0.01$). The total area under the concentration/time curve (AUC) increased from 8·7 (5·5) to 14·2 (9·3) μg/h ($p<0.01$) but mean urinary digoxin clearance remained unchanged (92/27) to 74·0 (34 1) ml/min, p = NS). In the six patients receiving maintenance treatment mean digoxin AUC remained increased at 16·7 (1·7) μg/h. Mean amiodarone plasma concentration at weeks 1 and 6 was 1·9 (0·5) and 2·2 (0·4) mg/l respectively. The addition of amiodarone treatment improved arrhythmia control in all patients; mean resting heart rate fell from 110 (10) to 65 (8) beats/min. Unwanted effects of combined treatment included bradycardia (2) and gastrointestinal upset (1), but exacerbation of arrhythmia was not seen.

Thus amiodarone substantially increases plasma digoxin concentrations and the results suggest an extrarenal mechanism. The magnitude of the interaction does not diminish during maintenance treatment.

A seven year experience with the St Jude medical valve

H O'Kane, D Gladstone, L Hamilton, J Cleland
Cardiac Surgical Unit, Royal Victoria Hospital, Belfast

From May 1979 until April 1986, 366 St Jude medical valves (143 aortic, 114 mitral, 53 multiple) were inserted in 310 patients (aged 5–82 years). The 30 day mortality was 1·4% aortic, 5·3 mitral, 9·4% multiple and the late mortality was 5% aortic, 6% mitral, and 1·9% multiple valve replacements. All patients were anticoagulated after operation. Two hundred and ninety eight patients have been followed for a total of 630 years. During that time we have not recorded a single occurrence of primary structural failure or significant haemolysis in any of the patients. One aortic valve patient stopped taking her anticoagulants and the valve became thrombosed. This valve was successfully replaced. In another patient the mitral valve became thrombosed after she switched from warfarin to subcutaneous heparin when she became pregnant; this valve was also successfully replaced. Thirteen patients experienced isolated thromboembolic episodes (7 major, 6 minor), an incidence of 2·0 events/100 patient years (2·3 mitral, 1·9 aortic, and 2·5 multiple). In 14 patients (7 mitral and 7 aortic) we measured the postoperative transvalvar gradients and effective valve areas. These studies confirmed the excellent haemodynamic function of this valve.

Our extended clinical experience of the St Jude medical valve, which has a low profile (especially in the mitral area), reduced thrombogenicity, and large effective area, makes it our prosthetic valve of choice.

Conversion of atrial fibrillation to sinus rhythm: evidence for delayed improvement in exercise capacity

D P Lipkin, M Frenneaux, R Stewart, Trudi Lowe, A Maseri
Royal Postgraduate Medical School, Hammersmith Hospital, London

We have assessed the effect on exercise capacity of restoration of sinus rhythm in patients with atrial fibrillation (AF) and controlled ventricular response. Ten patients (9 men) (mean age 56 years (range 36–74)) were studied. AF had been present for 6–14 weeks and was associated with aortic or mitral valve surgery (6), dilated cardiomyopathy (2), coronary artery disease (1); in one patient it was idiopathic. Resting LV ejection fraction was 38% (range 12–75). All subjects were practised in treadmill exercise before participating in the study. Treadmill exercise capacity was assessed by measurement of maximal oxygen consumption ($\dot{V}O_2max$) and anaerobic threshold by mass spectrometric analysis of mixed expired air before and on days 1 and 28 after elective DC cardioversion. Peak LV inflow velocities across the mitral valve were measured with pulsed Doppler. The relative contribution of atrial contraction to LV filling was determined by relating the areas under the A wave to the area under the E wave of the velocity time curve. $\dot{V}O_2max$ (ml/kg/min) on days 0, 1, and 28 was 21 (3), 21 (3), and 24 (4) respectively (day 0 + 1 *vs* 28, $p<0\cdot01$). Anaerobic threshold (ml/kg/min) on days 0, 1, and 28 was 17 (2), 16 (3), and 19 (2) respectively (day 0 + 1 *vs* 28, $p<0\cdot05$). Atrial contribution to LV filling was trivial or absent in all patients studied on day 1 and had increased significantly in all patients by day 28.

Conversion of AF to sinus rhythm is associated with a delayed improvement in exercise capacity. This may in part be due to slow improvement in atrial contractility and peak cardiac output after cardioversion.

Risk factors for the formation of left atrial thrombus in mitral valve disease: who should be anticoagulated?

I R Starkey, I Styliades, A Salachas
Cardiology Department, Northern General Hospital, Sheffield

A retrospective study of 256 consecutive open mitral valve operations performed in one hospital over a 33 month period has shown that 25 (9·8%) patients had thrombus in the left atrium at operation. In only four had the presence of thrombus been suspected at preoperative echocardiography. Significant risk factors for the presence of thrombus in the left atrium included predominant mitral stenosis, preoperative atrial fibrillation, and a history of "possible systemic embolism". No patient undergoing operation for dominant or pure mitral regurgitation of non-rheumatic origin had thrombus in the left atrium at operation. Thirty one of the 37 patients with a history of "possible systemic embolism" had rheumatic mitral stenosis, and all except one had suffered their possible embolic event before the start of anticoagulant treatment. Four were still in sinus rhythm *after* the presumed embolus and a further 11 valves embolised within one month of the onset of atrial fibrillation.

The results support the widespread use of early anticoagulant treatment in patients with rheumatic mitral valve disease, but suggest that such treatment may not be beneficial in patients with non-rheumatic mitral regurgitation.

Electrocardiographic findings in veteran athletes

S D Pringle, F G Dunn, A R Lorimer, P W Macfarlane
University Department of Medical Cardiology, Royal Infirmary, Glasgow, and Department of Medical Cardiology, Stobhill General Hospital, Glasgow

There have been few studies of ECG findings in highly trained veteran athletes (aged over 40 years). To assess the frequency of electrocardiographic abnormalities in this age group, the 12 lead electrocardiograms (and cross sectional echocardiograms) of 38 top ranking veteran athletes (15 long distance cyclists, 15 marathon runners, and 8 weight lifters; mean age 53·5 years, range 42–72 years) were studied. ECG measurements were made by computer and electrocardiographic left ventricular hypertrophy (LVH) was assessed by the Sokolow and Lyon (S-L) index ($SV1 + RV5 > 3\cdot5\,mV$) and by a modified Romhilt-Estes (R-E) scoring technique. Left ventricular mass measured by echocardiography was regarded as abnormal if it was $>215\,g$ or $140\,g/m^2$ when indexed by body surface area. ECG abnormalities were common: sinus bradycardia (less than 60 beats/min) occurred in 25; first degree atrioventricular block in three; second degree atrioventricular block (Mobitz type 1) in one; ST elevation in seven; T wave inversion in three; prolonged QTc in four. Thirty individuals had echocardiographic evidence of LVH by mass alone while only 14 had echocardiographic evidence of LVH by the indexed mass. Left ventricular function was normal in all subjects. The sensitivity and specificity for the S-L criteria with respect to LV mass were 20% and 75%. Corresponding figures for the R-E scoring technique were 27% and 75%. When the indexed LV mass was used, however, the sensitivity and specificity improved to 29% and 89% for S-L and 43% and 89% for R-E.

Thus it is concluded that ECG abnormalities are common in veteran athletes and that the specificity of ECG LVH criteria in this group is acceptable when measured against LV mass indexed for body surface area.

Perioperative acute myocardial infarction in coronary bypass surgery: is it related to preoperative ischaemia?

H Yousif, G J Davies, S Westaby, D Moss,
R Sapsford, C M Oakley
Department of Cardiology, Hammersmith Hospital,
London

One hundred consecutive patients undergoing coronary artery bypass grafting were randomly allocated to preoperative (24 h) intravenous infusion of isosorbide dinitrate (ISDN 1 5 mg/h, 50 patients) or to placebo (50 patients). The two groups were found to be closely matched (comparability 95%). The occurrence of transient acute myocardial ischaemia was established by continuous ECG Holter recordings (2 leads) with frequency modulated recorders. The diagnosis of myocardial infarction was based on the combination of clinical findings, ECG criteria (new Q waves), and serial creatine kinase MB isoenzyme concentrations. Episodes of acute myocardial ischaemia (rectilinear or down sloping ST segment depression $\geqslant 0{\cdot}1$ mV) were found in 18% of patients in the control group and in none of those who received ISDN ($p < 0{\cdot}02$). However, the incidence of perioperative infarction was similar (22% and 18% respectively). In this study a significantly higher frequency of perioperative myocardial infarction (PMI) was found in women (40%, $p < 0{\cdot}05$) (especially in those who were hypertensive (55%, $p < 0{\cdot}05$), patients with unstable angina (62·5%, $p < 0{\cdot}01$), patients with poor left ventricular function (39%, $p < 0\ 05$), those subjected to coronary endarterectomy (40%, $p < 0{\cdot}05$), and those in whom the aortic clamping time was $\geqslant 50$ min (37%, $p < 0{\cdot}05$). These factors may have obscured the effect on PMI of preventing preoperative ischaemia.

Our results show that preoperative ISDN infusion eliminates preoperative ischaemia but did not influence the occurrence of PMI. The probable benefits of prevention of preoperative ischaemia on postoperative left ventricular function, a determinant of long term survival, remain to be established.

Intravenous digital subtraction angiography in aortic root abscess

H Thomas, G J Hunter, T Treasure, R H Swanton
Middlesex Hospital, London

Aortic root abscess occurring in aortic valve endocarditis is a complication that usually requires urgent operation. The diagnosis of these abscesses has entailed formal arterial angiography, echocardiography, and computerised tomography. The most useful anatomical information is obtained from aortic root arteriography. There is a risk that friable infected material may be displaced from the affected valve and that perforation will disseminate the contents of the abscess cavity. Either may result in distant secondary abscess formation at any site. Three patients with aortic valve endocarditis (one with a prosthetic valve infected with *Staphylococcus epidermidis* and two with native valves infected with Streptococci of the viridans type) underwent intravenous digital subtraction angiography (DSA) immediately before operation. In two cases first degree heart block suggested the possibility of a septal abscess. DSA demonstrated a large paravalvar abscess in several projections in all cases. Subsequent operation confirmed the site and nature of the abscess cavity.

The technique of intravenous DSA with an injection of non-ionic contrast in the superior vena cava and imaging of the aortic root in at least two projections produces high quality diagnostic images, even in very sick patients. Disturbance of the abscess is avoided yet good anatomical information is obtained. The use of non-ionic contrast prevents percipitation of further cardiac decompensation, allowing detailed demonstration of the aortic root anatomy in several projections.

"Reperfusion" arrhythmias after ST segment depression on ambulatory monitoring in stable angina

G P Carboni, A Lahiri, P M M Cashman,
E B Raftery
Cardiology Department and Division of Clinical Sciences, Northwick Park Hospital, Harrow, Middlesex

The mechanism of arrhythmias that occur during and after episodes of transient myocardial ischaemia in man is unknown. In laboratory animals acute occlusion produces reentry, and reperfusion procedures enhanced automaticity. To test the hypothesis that both of these mechanisms are operational in man, we studied 33 patients with stable angina and obstructive coronary artery disease who were taking only sublingual nitrates. 24 hour ambulatory monitoring showed 115 episodes of ≥ 1 mm ST segment depression 80 ms from the J point lasting at least 3 min. In 11 of these patients 40 episodes were associated with arrhythmias. The total number of episodes was greater in the group with arrhythmias (6 (5) *vs* 2 (1), $p<0{\cdot}001$) as was the degree of duration of ST segment depression (2·8 (1·6) *vs* 1·9 (0·6) mm, 18 (15) versus 6 (3); $p<0{\cdot}001$). Serious arrhythmias (Lown 3–5) occurred only during ST segment depression and were closely related to severe asymptomatic and repetitive episodes. Arrhythmias occurring before and after peak ST segment depression were identified. Ventricular tachycardia occurred in three patients during the early phase of ischaemia and in the late phase in two. Ventricular tachycardia occurring during the early phase of ischaemia was associated with increased prodromal ectopic activity. That occurring in the late phase was not. Late arrhythmias were more frequent ($p<0{\cdot}001$) than early arrhythmias, with an increase in R on T ventricular extrasystoles. These differences suggest that reentry is responsible for early and enhanced automaticity for arrhythmias occurring in the late phase of ischaemia.

Quantifying clinical judgement: the prediction of coronary artery surgical mortality

I Graham, L Daly
The Irish Cardiac Surgical Register Group, c/o Adelaide Hospital, Dublin, Ireland

The Irish Cardiac Surgical Register is responsible for an independent evaluation of all open heart surgery performed on adults in the Republic of Ireland. The purpose of the present study was to derive a simple index to predict in hospital mortality for coronary artery bypass surgery (CABS) based on simple factors available before angiography. The effect of invasive investigations on risk prediction was also investigated. Forward stepwise logistic regression was used to derive an additive risk score based on the 976 CABS procedures (mortality 3·3%) performed in 1983/1984. The ability of this score to predict in hospital mortality was tested prospectively on the 699 CABS procedures (mortality 3·7%) performed in 1985. Of eight factors which appeared to predict increased mortality on univariate analysis, independent risk scores emerged as: age ≥ 60, 1; myocardial infarction in six weeks before operation, 2; cardiomegaly, 1; left ventricular failure, 1½. When these were applied to the 1985 data the observed and predicted mortalities were respectively: score 0, 1·5% and 1%; score 1–2, 4·4% and 3·6%; score 2½, 7·7% and 17·4%. The addition of investigative data did not appreciably improve predictive ability.

Simple clinical measurements available to a general physician before invasive investigation can predict the risk of in hospital CABS mortality.

Thrombolytic treatment in acute myocardial infarction: the scope in a district general hospital

J Jagger, R G Murray, E J Flint, M K Davies, W A Littler
East Birmingham Hospital, Bordesley Green East, Birmingham

Despite the interest in thrombolytic treatment in acute myocardial infarction, it has been reported that only a small minority (14%) of patients considered for thrombolysis would be suitable. To determine the demand for such treatment in a district general hospital, data were collected for patients admitted with chest pain to our coronary care unit over a six month period. Of 197 patients with chest pain 131 (67%) patients were proven to have acute myocardial infarction. Criteria for thrombolytic treatment included presentation within six hours of the onset of symptoms, ST elevation $\geq 0{\cdot}2$ mV in two or more ECG leads, and age ≤ 70 years. Sixty seven (51%) of the 131 patients with subsequently confirmed acute myocardial infarction were eligible for thrombolysis. Criteria for thrombolysis were not fulfilled in 41 patients with acute myocardial infarction: 17 (13%) presented later than six hours, 15 (12%) failed to meet the ECG criteria, and 9 (7%) were over 70 years. A further 12 (9%) patients were excluded for cardiogenic shock, two patients had peptic ulcers, one patient had sustained an acute myocardial infarction two weeks before, and data from eight patients were lost.

These results suggest that around 50% of patients with acute myocardial infarction and 34% of all patients presenting with chest pain would be suitable for thrombolytic treatment. These data do not support the view that such treatment may only be applicable to a small number of patients with acute myocardial infarction.

The role of verapamil with digoxin in atrial fibrillation: a physiological resetting of ventricular response

K J Hogg, R S Hornung, W S Hillis
University Department of Materia Medica, Stobhill Hospital, Glasgow

The control of the ventricular response in atrial fibrillation may remain difficult despite therapeutic concentrations of digoxin and may require the addition of a second drug. This study examines the kinetic and dynamic action of verapamil as second line treatment. Two different formulations were tested. Eleven patients (7 men and 4 women, mean age 60·4 (4·5) yr) with an uncontrolled ventricular response (heart rate >85 beats/min) despite steady state therapeutic digoxin (D) concentrations (0·8–2·0 ng/ml) were studied. 24 hour heart rate profile was assessed by Holter monitoring and this confirmed a rapid ventricular response during active hours (97 (13·5) beats/min) with nocturnal slowing (68 (15) beats/min). Ventricular response to symptom limited exercise showed peak heart rate of 161 (27) beats/min. Patients then entered a randomised crossover study with verapamil (V) and verapamil slow release (VSR). Both verapamil formulations were effective in reducing the ventricular response during active hours ($p < 0·002$) with no further nocturnal slowing. Baseline subtraction of the heart rate response demonstrated superimposition of the heart rate profile, suggesting resetting of the baseline with an intact incremental response to activity. Exercise capacity was not increased but V and VSR reduced peak exercise heart rate by 21·5%. The increment in heart rate (peak − baseline) was unaltered. The kinetic interaction produced only a minor rise in digoxin concentration from 1·28 (0·27) to 1·67 (0·6) on verapamil and to 1·51 (0·5) on verapamil slow release (NS).

These results suggest that verapamil is a safe and effective second drug in atrial fibrillation. It resets the heart rate to lower levels without a reduction in the incremental rise on activity, allowing these responses to occur within a more physiological range.

Obesity and the electrocardiographic diagnosis of left ventricular hypertrophy

J M McLenachan, E Henderson, K I Morris, H J Dargie
Cardiac Department, Western Infirmary, Glasgow

Criteria for electrocardiographic diagnosis of left ventricular hypertrophy (LVH) generally have high specificity but low sensitivity. It has been suggested that stratification of patients by age and sex will improve this sensitivity. We examined the influence of obesity on ECG diagnosis of LVH to determine whether knowledge of body build could further improve ECG performance for detection of LVH. Using sex specific upper limits of normal for left ventricular mass index derived from a control population, we found echocardiographic LVH in 61 of 100 hypertensive patients. Sensitivity values for chest lead (CL) criteria (SV1 + RV5 $>$ 35 mm), limb lead (LL) criteria (net positivity in I + net negativity in III >17 mm), and Estes point scoring system were 59%, 39%, and 41% respectively, with specificity values of 92%, 90%, and 90%. Of these 61 with LVH, 30 were obese as defined by weight $>120\%$ predicted weight by age, sex, and height. Sensitivity values in this group were 40%, 60%, and 33% respectively for CL, LL, and Estes; for non-obese hypertensive patients, equivalent values were 77%, 19%, and 48%. Thus limb lead criteria are more sensitive for detection of LVH in obese individuals in whom cardiac axis is directed more horizontally. When different criteria were applied to the two groups (LL to obese and CL to non-obese hypertensives), ECG sensitivity for LVH rose to 69% with specificity of 87%.

Thus stratification of patients by body build can increase the sensitivity of the electrocardiogram for the detection of left ventricular hypertrophy.

A comparison of atenolol and sotalol in the treatment of patients with paroxysmal supraventricular tachycardia

P M Schofield, F Reid, D H Bennett
Regional Cardiac Centre, Wythenshawe Hospital, Manchester

We compared the efficacy of sotalol (a β blocker with class III antiarrhythmic activity) and atenolol in a randomised crossover study of patients with frequent palpitation due to paroxysmal supraventricular tachycardia (SVT) (rate 142–231 beats/min) who had not previously received β blockers. Thirteen patients, aged 20–65 years, received treatment with atenolol (50 or 100 mg daily) for six weeks and sotalol (120 or 240 mg daily) for six weeks. Patients used hand held ECG recording devices to record the cardiac rhythm at the time of symptoms during each treatment period and the number, total duration, and mean duration of attacks of SVT were documented. Two patients had prolonged episodes of SVT while receiving atenolol and did not complete this treatment period. Three patients had no symptoms during either treatment period. A further five patients were free of palpitations only while receiving sotalol and one patient only during treatment with atenolol. The number of episodes of SVT was significantly lower during treatment with sotalol (median 0, range 0–22) than with atenolol (2, 0–26) ($p<0.05$). During treatment with sotalol the total duration of SVT (0 min, 0–55 min) and the mean duration of each episode (0 min; 0–3·5 min) were significantly lower than with atenolol (45 min, 0–390 min) ($p=0.01$) and 6 min, 0–195 min ($p=0.02$) respectively.

In patients with paroxysmal SVT treatment with sotalol results in better control of symptoms than treatment with atenolol.

Use of amiodarone to maintain sinus rhythm after cardioversion for atrial fibrillation

E J Ladusans, D Holt, P V L Curry
Cardiac Department, Guy's Hospital, London

To assess the efficacy of amiodarone in maintaining sinus rhythm after DC cardioversion for atrial fibrillation (AF), 11 consecutive patients who relapsed into AF after an initially successful primary cardioversion to sinus rhythm were given amiodarone before a second DC shock. AF was secondary to cardiomyopathy in five, to rheumatic heart disease in four, and idiopathic in two. These patients form part of a continuing prospective study; so far 30 patients have undergone primary cardioversion. Amiodarone was given in an initial dose of 200 mg three times a day for one week and 200 mg twice daily thereafter until the measured plasma concentration was in the range 1–1·5 μg/ml before the second cardioversion. Amiodarone was continued after successful cardioversion in an average maintenance dose of 200 mg daily. Two patients reverted spontaneously to sinus rhythm after starting amiodarone (plasma concentration 1·0 and 1·2 μg/ml). In two patients amiodarone had to be discontinued before a second cardioversion could be performed; in one because of a rash and in the other because of a junctional bradycardia. The mean (SD) duration of sinus rhythm after the primary cardioversion was 1·5 (1·3) months, and 5·8 (4·9) months after amiodarone four remain in sinus rhythm (follow up 1–14 months).

We conclude that amiodarone is effective in prolonging the duration of sinus rhythm after repeat DC shock in those patients with AF who relapse after successful primary cardioversion. Toxicity may limit its use, however.

Sexual dysfunction before and after coronary artery bypass surgery

C Bass, F Akhras, J Upward, J Keates, G Jackson
Cardiac Department, King's College Hospital, London

Eighty eight patients (78 men) were prospectively studied before and 12 months ($n = 81$) after coronary artery bypass surgery. They were asked about the presence of sexual dysfunction at both interviews. Twelve (14%; 11 men) reported sexual dysfunction before operation. Nine reported erectile difficulties and another three (one woman) loss of sexual desire. Thirty four (39%) patients had not engaged in sexual relations for at least six months before operation and the remaining 42 (48%) reported no sexual difficulties. The duration of preoperative anginal symptoms was shorter in the 12 patients with problems than in those without sexual problems (26 (7·5) months *vs* 48·5 (5·8), $p<0.05$), but there were no other significant differences in other physical or psychological variables. All those with sexual problems before operation continued to have similar difficulties 12 months afterwards. Only two patients reported sexual problems precipitated by operation.

We conclude that before operation 1 in 7 patients had sexual dysfunction severe enough to prevent intercourse. Only rarely does operation have any adverse effect on sexual function. It does not ameliorate established sexual problems, however. Specific counselling should be routine before and after cardiac surgery.

Magnetic resonance blood flow patterns in the human aorta

R H Klipstein, D N Firmin, S R Underwood,
R S O Rees, D B Longmore
Magnetic Resonance Unit, Britten Street, London

Magnetic resonance velocity mapping non-invasively produces two dimensional profiles of blood velocity and provides potentially important information on function. This study defines normal profiles in the ascending aorta and descending aorta in man. Maps of the craniocaudal component of blood velocity were obtained in 12 healthy volunteers in a transverse plane 5 cm above the aortic valve, through which the ascending and the descending aorta passed perpendicularly. Cine images were acquired with a temporal resolution of 50 ms and a pixel size of 1·8 × 1·8 mm. In all subjects plug flow occurred during systole, but the ascending aortic velocity profile was skewed. Turbulent flow never occurred. Mean (SD) duration of plug flow was 117 (26) ms in the ascending aorta and 126 (22) ms in the descending aorta. During diastole, blood was not static, but circulated within the ascending aorta, with forward flow at the anterolateral wall and reverse flow at the posteromedial wall. A similar pattern was seen in the descending aorta.

These results demonstrate a highly consistent but complex pattern of aortic blood flow in health. During diastole, channels of forward and reverse flow occur in the same vessel.

An objective method for assessing right ventricular systolic and diastolic function in patients with coronary artery disease

E A Rodrigues, I M Al-Khawaja, A Lahiri,
E B Raftery
Department of Cardiology, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex

Gated blood pool angiography (GBPA) has been widely used to arrive at sophisticated indices of left ventricular function, but assessment of right ventricular (RV) function has been limited to measurement of the ejection fraction (EF). We have developed an automated method for assessing RV function from GBPA with technetium-99m and the technique has been used to study 40 normal subjects and 30 patients with chronic stable angina. ECG gating was used to collect data in 32 frames/cardiac cycle with 5% gate tolerance. A second derivative method of edge detection was used to define the RV contour and to delineate tricuspid and pulmonary valve planes in each of the frames by local threshold methods. A high resolution time-activity curve was then obtained and a first derivative sample was generated to identify the points of peak filling and emptying. The mean (SEM) normal resting values were: EF 44 (1·4)%, ejection rate (ER) 1·5 (0·06) EDV/s, ejection time (ET) 310 (7) ms, peak filling rate (PFR) 2·0 (0·08) EDV/s, time to peak filling rate (TPFR) 180 (10) ms, filling fraction (FF) 0·5 (0·04). In the patients the values were: EF 42 (1·8) (p = NS), ER 1·2 (0·06) ($p < 0·005$), ET 360 (10) ($p < 0·001$), PFR 1·8 (0·09) (p = NS), TPFR 152 (12) (p = NS), FF 0·5 (0·02) (p = NS). Exercise EF was similar in both groups but exercise ER, ET, and PFR were significantly higher in normal subjects ($p < 0·001$, $p < 0·02$ respectively). The reproducibility of the technique was good ($r = 0·95$; $p < 0·002$).

RV function can be usefully and reproducibly assessed from GBPA, and ER and ET may be more sensitive indices for assessing RV systolic function than just EF alone.

The echocardiographic Doppler description of pericardial prostheses and the potential in long term follow up

P Nihoyannopoulos, R A Foale, Gillian C Smith,
Celia M Oakley, K M Taylor
Hammersmith Hospital, Royal Postgraduate Medical School, London

Forty two consecutive patients who underwent valve replacement with a bovine pericardial xenograft (PX) were prospectively studied by cross sectional echocardiography and colour Doppler flow mapping to evaluate the potential of the technique for long term follow up and early detection of PX dysfunction. Twenty patients had aortic valve replacement (AVR), 17 had mitral valve replacement (MVR), and five had AVR and MVR valve replacements. Doppler-echocardiographic studies were performed immediately after operation, at 6 months, and then every year. During a follow up lasting 2 months to 4 years (mean 3·2 years) details of PX leaflet motion were recorded and PX leaflet thickening and orifice area were measured. In most (86%) patients the PX leaflet motion was symmetrical, leaflet thickness measured 1–4 mm, and eccentricities in appearance were common. There was no significant change in leaflet configuration between studies. These appearances were associated with normally functioning PX. Three patients had early prosthetic endocarditis that was treated successfully. Flow mapping Doppler demonstrated laminar flow across all PXs and a mild PX leak in two patients with MVR and one with AVR. Peak velocities across all PXs were similar to those of normal native valves. Mitral valve orifice areas of PX were similar in size to the prosthesis implanted.

Over short follow up, unchanged leaflet configuration and function implies satisfactory PX function and serial studies to detect changes from baseline may help to identify promptly PX leaflet degeneration. The real time display of the aortic or mitral regurgitant jet seems greatly to facilitate this application of colour Doppler flow mapping and is a valuable adjunct to the non-invasive assessment of PX.

Myocardial architecture of right ventricular hypertrophy

R A Greenbaum, D G Gibson, M H Yacoub,
R H Anderson
Harefield Hospital, Brompton Hospital, and
Cardiothoracic Institute, London

Normal ventricles show pronounced regional variations in structure. The purpose of the current study was to identify the architectural features of right ventricular hypertrophy. Six hearts were studied from patients with primary pulmonary hypertension undergoing heart lung transplantation. Ventricular architecture was studied by inspection of the orientation of superficial fibres and dissection to show structure within the wall. There were major departures from normal anatomy. The acute margin was about 40% longer than the obtuse margin. The right ventricular vortex was considerably enlarged and formed the apex. The septum "belonged" to the right ventricle and bulged into the left ventricular cavity. There were changes in muscular fibre orientation. The uppermost fibres on the acute margin ran longitudinally; further down they passed more obliquely and on to the sternocostal aspect. The lowermost fibres formed the apex. The wall of the right ventricle was thickened, chiefly due to the presence of a well developed middle layer of fibres, which were absent in the normal heart. On the diaphragmatic aspect these fibres ran circumferentially to the inlet long axis: the orientation altered on the acute margin so that on the sternocostal aspect they came to lie circumferentially to the outlet long axis. The middle layer was best developed towards the base. The subendocardial fibres were longitudinal on the diaphragmatic aspect. In the infundibulum they were circumferential: on the sternocostal aspect they had various orientations.

These differences from normal architecture provide an anatomical basis for the high systolic pressure generated by the right ventricle in primary pulmonary hypertension.

Br Heart J 1987;57:109–10

Correspondence

Heart rate variability in healthy subjects: effect of age and derivation of normal ranges for tests of antonomic function

Sir,

The study on the effect of age on heart rate variability in normal subjects by O'Brien *et al* (1986;55: 348–54)[1] deserves comment.

(*a*) The confidence limits obtained are lower than in previous studies. This is attributed to the larger number and more uniform age distribution of the subjects. Differences in selection criteria and test procedures are, however, another explanation. More information should, therefore, be provided on the subjects and test conditions such as values for resting heart rate, supine blood pressure, the time of the day the experiments were performed, and the intake of coffee and cigarettes before the experiments.[1]

(*b*) Information is not given on the period of supine rest before the patient stood up. This is an important omission since we have shown that the duration of rest before standing has a profound (20–40%) influence on the magnitude of the initial heart rate response induced by standing up.[2–4]

(*c*) The instant at which the initial peak heart rate increase evoked by standing up was observed by O'Brien *et al* seems to have occurred earlier than we found in our studies.[2 3 5] This is not surprising since the recording was not started at the onset of standing up,[2] but at the moment the subject became erect. The latter procedure is not correct from a physiological point of view.[3]

(*d*) I agree that cardiovascular autonomic function should be assessed by a combination of tests and that the establishment of normal ranges in relation to age is also important. But ultimately an understanding of the physiological mechanisms involved is the most important factor.[3 5 6]

Unfortunately, O'Brien *et al* leave us with much numerical information, but little physiological interpretation.

W Wieling,
Department of Medicine,
Academic Medical Centre,
Meibergdreef 9,
1105 AZ Amsterdam,
The Netherlands.

References

1 O'Brien IAD, O'Hare P, Corrall RJM Heart rate variability in healthy subjects. effect of age and the derivation of normal ranges for tests of autonomic function. *Br Heart J* 1986;55:348–54.
2 Wieling W, van Brederode JFM, de Rijk LG, Borst C, Dunning AJ. Reflex control of heart rate in normal subjects in relation to age: a data base for cardiac vagal neuropathy. *Diabetologia* 1982,22:163–6.
3 Borst C, Wieling W, van Brederode JFM, Hond A, de Rijk LG, Dunning AJ Mechanisms of initial heart rate response to postural change. *Am J Physiol* 1982;243:H676–81.
4 Borst C, van Brederode JFM, Wieling W, van Montfrans GA, Dunning AJ. Mechanisms of initial blood pressure response to postural change. *Clin Sci* 1984;67:321–7
5 Wieling W, Borst C, van Lieshout JJ, *et al.* Assessment of methods to estimate impairment of vagal and sympathetic innervation of the heart in diabetic autonomic neuropathy. *Neth J Med* 1985,28.383–92
6 Bennett T. Physiological investigation of diabetic autonomic failure. In. Bannister R, ed. *Autonomic failure A textbook of clinical disorders of the autonomic nervous system.* Oxford: Oxford University Press, 1983:337–70

This letter was shown to the authors, who reply as follows:

Sir,

We are grateful for Dr Wieling's comments but feel that he may have misinterpreted the purpose of our study: this was to provide a practical and reliable basis for the detection of impaired heart rate variability, not a physiological interpretation of our tests. These are used widely in routine clinical practice under uncontrolled conditions. We choose, therefore, to investigate normal subjects under similar circumstances, not under carefully controlled laboratory conditions. Heart rate variability is subject to a host of environmental, psychological, and neurohormonal influences that all contribute to the large coefficients of variation observed with these tests.[1 2]

Subjects were tested between 9 am and 5 pm. Resting heart rate was recorded after 5–10 minutes of supine rest and only when the usual initial fluctuations in heart rate had subsided. No restrictions were imposed on consumption of coffee or cigarette smoking. While this may have influenced the results, so may other factors such as the time from the last meal, anxiety level, room temperature, etc, etc. All subjects were supine for 10–20 minutes before standing, thus it is unlikely that the results would be spuriously low.[3] It is unrealistic to expect the timing of peak heart rate on standing to occur within a narrow range in 500 subjects. Our only comment on the latency of the heart rate changes on standing was that they are not accurately represented by the 30:15 ratio.

I A D O'Brien,
R J M Corrall,
Department of Medicine,
Bristol Royal Infirmary,
Bristol BS2 8HW.

References

1 Smith SA, Smith SE. Reduced sinus arrhythmia in diabetic autonomic neuropathy. *Br Med J* 1983; **286**:723.
2 Smith SA. Diagnostic value of the Valsalva ratio reduction in diabetic autonomic neuropathy; use of an age related normal range. *Diabetic Medicine* 1984;1: 295–7.
3 Wieling W, Borst C, van Lieshout JJ, *et al*. Assessment of methods to estimate impairment of vagal and sympathetic innervation of the heart in diabetic autonomic neuropathy. *Neth J Med* 1985;28:383–92.

Notices

British Cardiac Society

The Annual General Meeting for 1987 will take place in Dundee on 8 and 9 April 1987, and the closing date for receipt of abstracts will be 6 January 1987.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

Electrocardiology

The 14th International Congress on Electrocardiology will be held in East Berlin on 17 to 20 August 1987. Details from: Dr Peter W Macfarlane, University Department of Medical Cardiology, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER, Scotland.

Br Heart J 1987;57:111–2

CHECKLIST

Please make a photocopy of this checklist, complete, and send with all manuscripts submitted for publication.

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☐Two complete sets of the manuscript (including 2 sets of figures) are submitted.

☐The manuscript is typed double spaced throughout on one side only on 22 × 28 cm (8½ × 11″) opaque white bond paper with 3 cm margins all around.

☐The manuscript is arranged as follows: (1) title page, (2) summary, (3) text, (4) references (5) legends, (6) tables. Pages are numbered consecutively, beginning with the title page as page 1.

☐The last name of the first author is typed at the top right corner of each page.

Title page

☐The title and authors' names with symbols (* † ‡ etc) to indicate place of appointment are typed on the title page.

☐No more than three authors' names should be given for case reports.

☐The name and address of the institutions from which the work originated are included.

☐The full name, exact *postal* address with postal code, and telephone number of the author to whom communications, proofs, and requests for reprints should be sent are typed at the bottom.

Summary

☐A summary (excluding statistical analyses) is typed double spaced on a separate page.

☐The summary is substantive rather than purely descriptive.

☐Abbreviations other than standard units of measurement are not used.

Text

☐Abbreviations or acronyms are always written out in full (for example, ECG, electrocardiogram; LVH, left ventricular hypertrophy; CAD, coronary artery disease, MI, myocardial infarction).

☐Only units of measurement and mathematical formulas and calculations are abbreviated and they follow the form recommended in *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (*Br Heart J* 1984; **51:** 1–6).

☐Appropriate headings and subheadings are provided.

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☐Abbreviations of journals conform to those used in *Index Medicus,* US National Library of Medicine. The style and punctuation of the references follow the format illustrated in the following examples:

Journal: (list *all* authors if six or less; otherwise list first three and add *et al*; do not use full stops after authors' initials)

31 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary angio-

graphic findings. *Br Heart J* 1984; **52:** 304–8.

Chapter in book:

28 Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. *Heart disease in infants, children and adolescents.* Baltimore: Williams and Wilkins, 1968: 134–9.

Book (personal author or authors): (all book references should have specific page numbers)

36 Feigenbaum H. *Echocardiography.* 3rd ed. Philadelphia: Lea and Febiger, 1981: 549–63.

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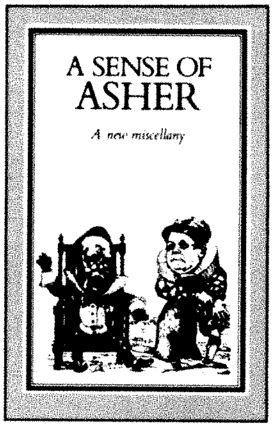

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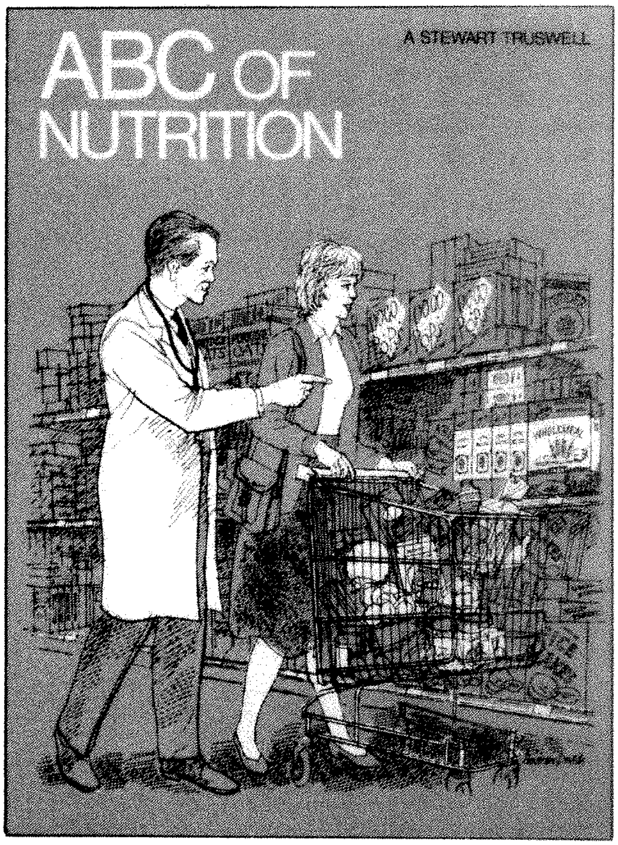

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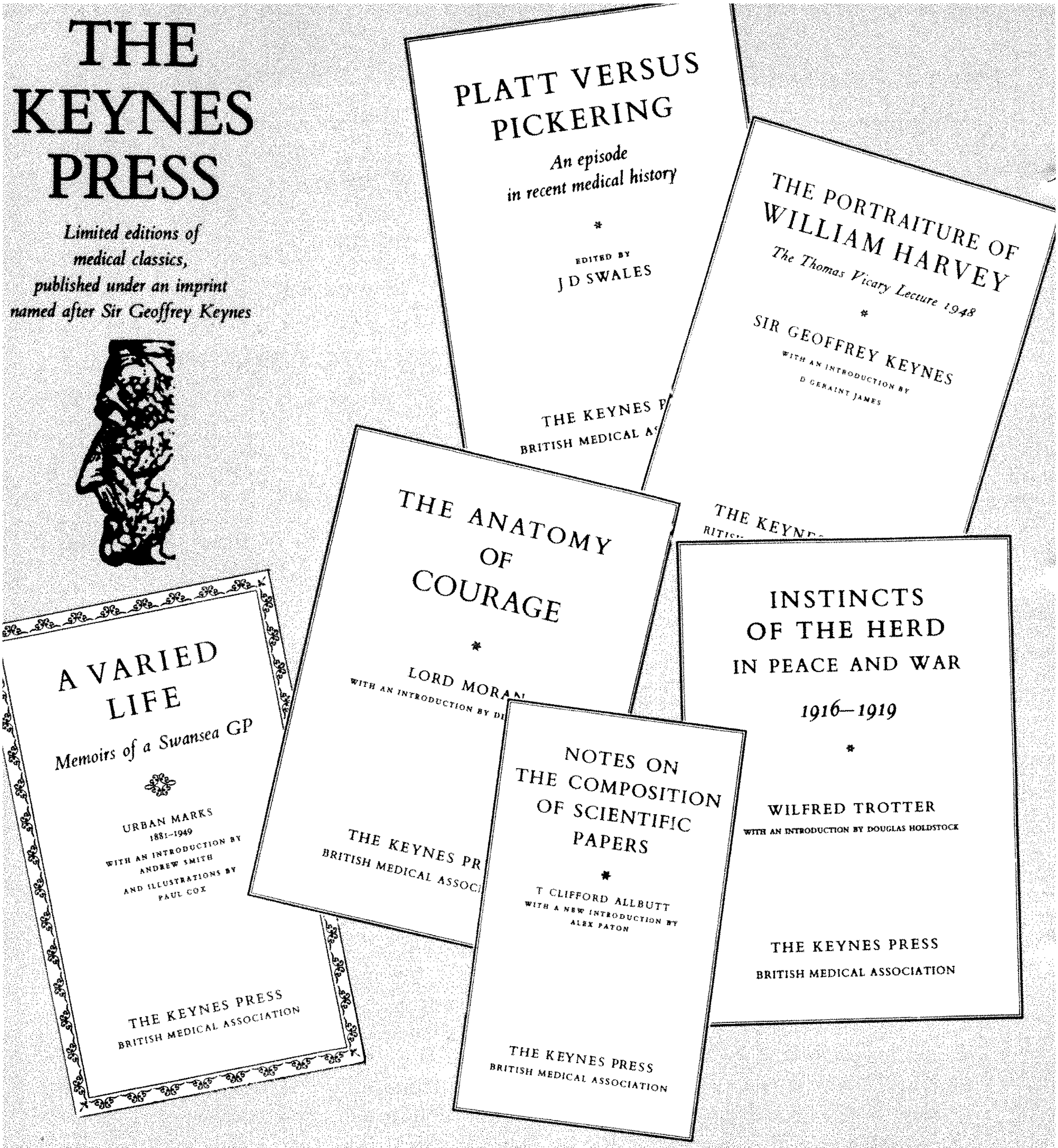

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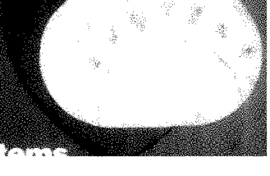

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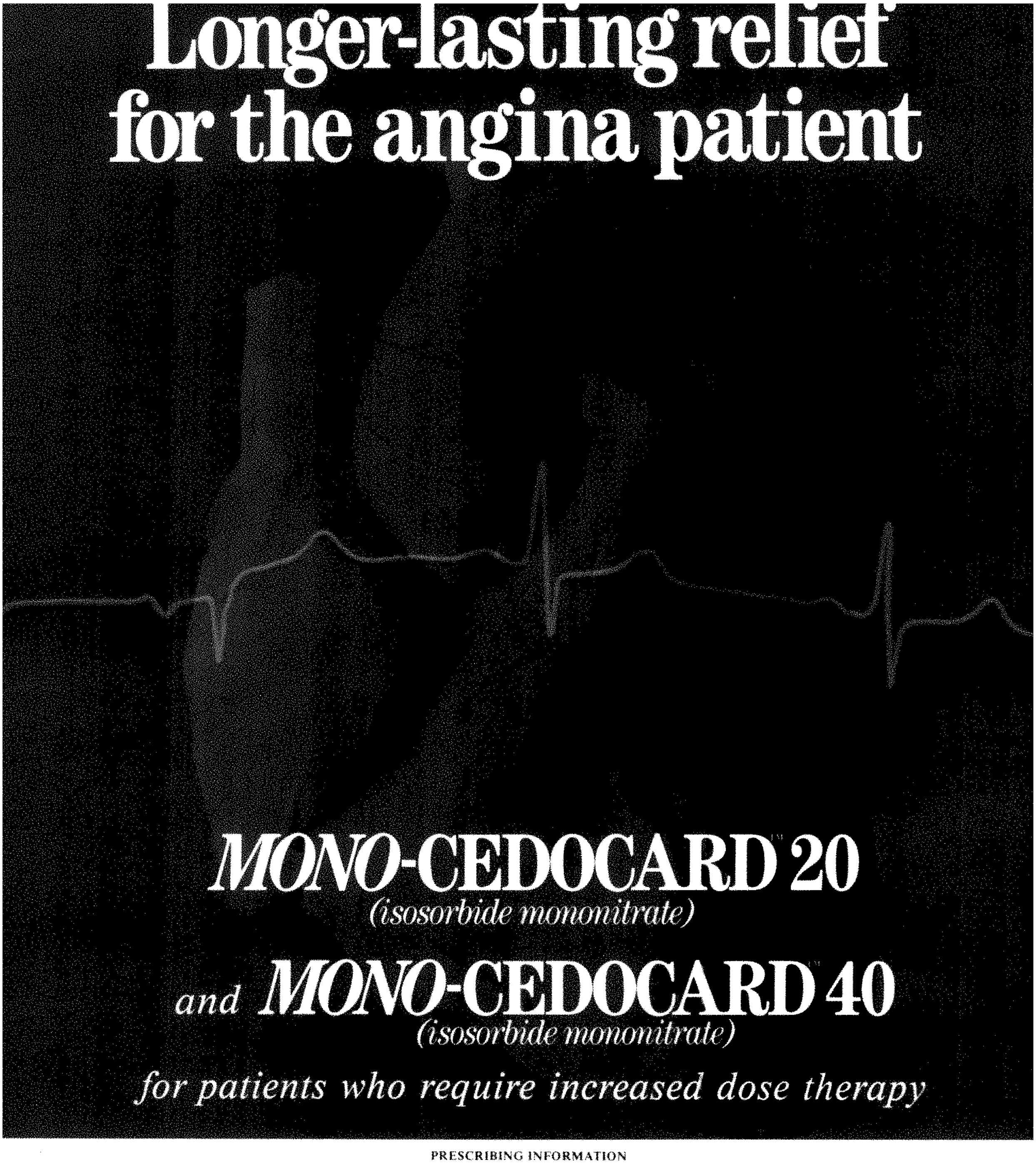

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Br Heart J 1987;57:113–7

Jubilee Editorial

Electrocardiography then and now: where next?

DENNIS M KRIKLER

From the Division of Cardiovascular Disease, Royal Postgraduate Medical School, Hammersmith Hospital, London

When the Cardiac Society of Great Britain and Ireland met for the first time its initial task was to set up a committee to define the best location for a single chest electrocardiograph lead. The recommendations were agreed with the American Heart Association and a joint report was published in both countries and republished in the first issue of the *British Heart Journal.*[1] At that time the electrocardiograph was the specialised investigation in cardiology; indeed it was the first clinical tool to become an essential component of cardiac practice since the introduction of the stethoscope, ophthalmoscope, and sphygmomanometer. An indication of its importance is its predominance in the first volume of the *British Heart Journal*, published in 1939. Of the 23 original articles that appeared that year, the electrocardiograph was the topic, or an important feature, in 12. Its importance remains undiminished. As Fisch has reminded us[2]: it is a non-invasive technique that does not harm the patient; it is inexpensive, simple, and reproducible; it permits serial studies to be made; and provides the only practical means of recording the cardiac action potential. It has several other virtues: it provides an independent marker of myocardial infarction, and enables one to undertake complex electrophysiological analysis through deductive reasoning.

Fifty years before the transformation of the Cardiac Club into the British Cardiac Society, Augustus Desiré Waller recorded the first electrocardiogram in man, using a Lippmann capillary electrometer.[3] Though this technique was impracticable for clinical use, this observation led to the introduction by Einthoven of his string galvanometer as a clinical instrument.[4] This aspect is more fully discussed by Howard Burchell on page 190 of this issue. Once Einthoven had established the basis, he selected the Cambridge Scientific Instrument Company of England as the original manufacturer.[5]

Much of the early work on the interpretation of electrocardiograms was carried out by Sir Thomas Lewis in London. Though not the first book on the subject, Lewis's was most influential[6]; and the third edition of his *The Mechanism and Graphic Registration of the Heart Beat* remains a comprehensive testament to the excellence of his work.[7] Lewis's researches on electrocardiography ended by 1923, though W H Craib carried out electrocardiographic research in his laboratory for another couple of years.[8] Sir Thomas took little direct interest in this work, and it came to a halt after Craib had important disagreements with a number of established authorities, notably Lord Adrian.[9]

The end of the Lewis era

Why did Lewis discontinue his research interests at that stage? It is widely thought that he gave them up because he grew tired of tackling the kinds of questions the instrument could answer and longed for the adventures suggested by his own mind.[10] Drury[11] gave two reasons: Lewis felt that a problem should not be taken up unless it could be carried through; otherwise the researcher would only "foul the nest". He also believed that if one had the capacity "one should try and skim the cream off the milk and leave the skim to others". Lewis's own earlier comments, however, suggested that, at the age of 43, he had become weary of being tied to an elaborate instrument and that he had come to the natural end of his studies on the disordered action of the heart.[12] Paroxysmal tachycardia eluded him because it could not then be produced experimentally, and he had great intuition in foreseeing what problems a certain method was capable of solving. Certainly intracardiac electrography and programmed stimulation later provided the tools to explain arrhythmias, very

Requests for reprints to Dr Dennis M Krikler, Division of Cardiovascular Disease, Hammersmith Hospital, 150 Ducane Road, London W12 0HS.

much in the terms that he had already predicted. Lewis had never explored the importance of the electrocardiograph in the study of ischaemic heart disease, nor did he do so in the next few years, when the early observations of Pardee[13] were extended and further analysed, especially by Levine.[14]

British cardiologists stepped back from greater involvement in research in electrocardiography at the very time when others, notably David Scherf,[15] then of Vienna, and Lewis's own good friend and fellow bird-watcher, Frank N Wilson, of Ann Arbor, Michigan, were enhancing its dimensions.[16] Wilson recognised the dependence of his dipole theory on the basic work of Craib,[9] who had called the same phenomenon "the doublet" a few years earlier.[17] But many papers from British institutions appeared, covering a host of aspects. To take two examples of such groups, both Wood and Selzer[18] and Evans[19] took a practical interest in electrocardiography. Both groups strongly favoured the use of specific bipolar (CR) chest leads, but Wilson's unipolar chest leads gradually prevailed—though as late as 1939 he was a co-signatory to the recommendation of a single bipolar chest lead.[1]

When the Cardiac Society was established the electrocardiograph was either hospital based or used in the consulting room. The development of portable apparatus, battery operated in some cases, allowed it to be taken to the patient's home. This was at first somewhat impractical because the photographic recordings had to be developed, though with some machines this could be done on the spot.[20] The first direct-writing units were becoming available (not always with enhancement of the quality of the tracings) but they only became more widely used from 1950 onwards.

Newer applications

At this stage the electrocardiograph had achieved considerable practical value in the diagnosis of cardiac ischaemia, notably myocardial infarction, and simple exercise tests aimed at reproducing angina and displaying ST segment changes had been introduced.[21] Arrhythmias could be diagnosed only on recordings made at the time of an attack—long term ambulatory tracings were yet to come. Conduction defects were better defined—the patterns of right and left bundle branch block were now correctly appreciated and the misunderstandings based on earlier observations in canine studies had long been rectified[22]—but the significance of conspicuous left or right axis deviation as possible markers of impaired conduction in the left bundle branch system was not yet recognised.[23] The principles of vectorcardiography, a technique which never achieved widespread independent application, had an important impact on this aspect of electrocardiography.

Parkinson was among the original authors of the classic paper on pre-excitation[24] though an earlier case, the first ever reported, also exemplified Anglo-American collaboration.[25] British electrocardiographers were well aware of the pattern of the Wolff-Parkinson-White syndrome.[26] Criteria for ventricular hypertrophy were still to be established though the studies of Wood and Selzer[18] had led to tentative answers. The intricate analysis of the electrocardiogram, to which Lewis had paid so much attention, received further consideration elsewhere and concepts such as concealed conduction, aberration, and overdrive suppression that can be identified in Lewis's early writings were amplified by workers in other countries. Many of them were continental cardiologists who had emigrated to the United States to escape persecution. Among those who made their home in Britain were Adolf Schott, who collaborated closely with Scherf,[27] and Cornelio Papp, a former assistant editor of the *British Heart Journal*. They played a crucial role in the teaching of electrocardiographic advances.

Intracardiac electrocardiography and electrophysiological testing

Intracardiac electrocardiography was first carried out in France during the second world war[28] and extended over the next two decades in the Netherlands.[29] The first clinical intracardiac recording of activity of the bundle of His was, however, reported from Dundee in 1967.[30] Once the techniques had become refined and standardised,[31] intracardiac electrography and programmed electric stimulation of the heart proved to be valuable research tools with wide application to the study of arrhythmia and conduction disturbance (linked with the development of cardiac pacemaking).[32 33] So where do we stand on these and related issues now, more than 15 years after programmed stimulation became generally available?

Originally it seemed likely that intracardiac recording techniques would prove helpful in the diagnosis of those at risk of sinoatrial or advanced atrioventricular block; however, they have served to point the way rather than precisely to define those likely soon to need pacemakers. None the less, knowledge from such studies has added to the general body of information, including that based on sound history taking and identification of lesser degrees of conduction impairment on the electrocardiogram, and this has helped to restore decision-making to the clinician.[34 35] Tests of sinus node performance—for example overdrive pacing of the atrium in order to assess sinus node recovery time or measurement of conduction between stimulated atrium and the sinus node—have enhanced our knowledge of sinus node behaviour and established the relatively benign prognosis of pure sinus node block: however, this technique usually only identifies patients in whom the disorder could otherwise be detected more simply.[36] Epidemiological studies have aided us in focusing on population groups who are more susceptible to sinus node disease and on the prognosis in atrioventricular block.[37] The electrophysiological discrimination between carotid sinus hypersensitivity and sinus node disease has, however, proved elusive.[38] The overlap between these two entities may well be responsible for such difficulties.

Antiarrhythmic agents

Reentrant atrioventricular tachycardias, whether intranodal or associated with an accessory atrioventricular pathway, have provided a rich harvest for electrophysiological investigators. The clinical value of such studies is already demonstrable in those few patients who may need invasive treatment,[39] which now includes antitachycardia pacing devices or surgical or endocavitary ablation of normal conducting tissue or an accessory pathway. Much has been gleaned of pharmacological values. It has been possible, for example, to demonstrate that the atrioventricular node is the site of action when such arrhythmias are terminated by calcium antagonists,[40] and thus to corroborate hypotheses based on knowledge of the cellular properties of such agents and on electrocardiographic findings.[41] Indeed it has been possible to discriminate between electrophysiologically active calcium agents and those that lack such properties at the clinical level,[42] but prediction of prophylactic value has also been elusive. Again, empirical observations have added to the knowledge that enables us to choose agents on a clinical basis—a term that includes the use of the surface electrocardiogram.

Electrophysiological studies have also improved the diagnosis of such arrhythmias. Wellens, in particular, has shown how programmed stimulation has generated important information that has enhanced the level of electrocardiographic analysis of arrhythmias.[43] Thus in most patients with paroxysmal atrioventricular tachycardia, electrophysiological study can be withheld unless standard medical management fails, and precise knowledge of the anatomy of the atrioventricular connection, including its location and the possibility of multiple links,[44] is required before the use of a pacing device, ablative technique, or surgical operation is considered. But this is not to deny the relevance of including questions of research importance when performing such studies. We need to know more about atrioventricular nodal function and whether the dual nodal pathways that are responsible for arrhythmias have an undiscovered anatomical basis or represent derangements of physiological function—perhaps of an interplay between autonomic factors, neuropeptides, and purines.[45]

Such studies are also needed to explain the basis for operations on the surface of the atrioventricular node that appear to prevent such arrhythmias[46] and thus to answer the important anatomical question that has never been resolved to the satisfaction of all workers—are such arrhythmias purely intranodal or is adjacent atrium an essential component of the circuit?[47 48]

Ventricular arrhythmias

Supraventricular tachycardias are straightforward compared with the questions prompted by ventricular arrhythmias and the resuscitation of those who had apparently dropped dead. There is much contention as to whether groups at risk of sudden death are reliably defined and their prognosis improved by electrophysiological testing.[49] Criteria for standardised testing in ventricular arrhythmias have been defined and agreed.[50] These rules can be followed by others, but the question that remains unanswered, after more than a dozen years of worldwide investigation, is the value of electrophysiological testing in this condition and in choosing appropriate medications to prevent ventricular tachycardia.[51 52] In other conditions we can rely more on the electrocardiogram and at least test its ability to teach us the essentials. Its potential usefulness in discriminating among patients who have right ventricular abnormalities, that is between those with a benign prognosis and those at risk of arrhythmia and possible sudden death, is intriguing.[53] The additional presence of visible late potentials in the surface electrocardiogram of some of these cases may well link up with related observations after acute myocardial infarction.[54]

Back to the electrocardiogram

The electrocardiogram—one hundred years old—is indeed a classic,[2] though not in the clinical form that we know. The string galvanometer and its successors have been cardiological tools for 80 years and the subject of fundamental contributions to the Cardiac Club, British Cardiac Society, and *British Heart Journal*, and, more extensively, to other learned societies and publications throughout the world. Interestingly, however, the basic principles are little different from those used by Sir Thomas Lewis. He might have been surprised that there was more to be learnt, and gratified that serious workers in this field still consult his writings[7] before describing apparently new disorders of rhythm or conduction.[55]

References

1 Memorandum by the Cardiac Society and the American Heart Association. Praecordial leads in electrocardiography. *Br Heart J* 1939;1:45–8

2 Fisch C. The clinical electrocardiogram: a classic. *Circulation* 1980;62 (suppl III):1–4.

3 Waller AD A demonstration on man of electromotive changes accompanying the heart's beat. *J Physiol* 1887;8:229–34.

4 Einthoven W. The string galvanometer and the human electrocardiogram. *K Akad Wet Amst Proc Sect Sci* 1903–4;6:107–15.

5 Burnett J. The origins of the electrocardiograph as a clinical instrument. *Med Hist* 1985;suppl 5:53–76.

6 Lewis T. *Clinical electrocardiography*. London: Shaw and Sons, 1913.

7 Lewis T. *The mechanism and graphic registration of the heart beat*. 3rd ed. London: Shaw and Sons, 1925.

8 Craib WH. *The electrocardiogram*. Medical Research Council special report series, No. 147. London: His Majesty's Stationery Office, 1930.

9 Pruitt RD, Doublets, dipoles and the negativity hypothesis: an historical note on W. H. Craib and his relationship with F. N. Wilson and Thomas Lewis. *Johns Hopkins Med J* 1976;138:279–88.

10 Pickering GW. Thomas Lewis 1881–1945. *University College Hospital Magazine* 1955;40:68–70.

11 Drury A. Thomas Lewis 1881–1945. *University College Hospital Magazine* 1955;40.70–1.

12 Drury AN, Grant RT. Sir Thomas Lewis. Obituary notices of fellows of the Royal Society 1945; 5:179–202.

13 Pardee HEB. An electrocardiographic sign of coronary artery obstruction. *Arch Intern Med* 1920;26:244–57.

14 Levine SA. *Coronary thrombosis: its various clinical features*. London: Ballière, Tindall and Cox, 1929: 66–94.

15 Scherf D. A cardiologist remembers. *Perspect Biol Med* 1968;11:615–30.

16 Johnston FD, Lepeschkin E, eds. *Selected papers of Dr Frank N. Wilson*. Ann Arbor, Michigan: JW Edwards, 1954.

17 Craib WH. A study of the electrical field surrounding active heart muscle. *Heart* 1927;14:71–109.

18 Wood P, Selzer A. Chest leads in clinical electrocardiography. *Br Heart J* 1939;1:49–80.

19 Evans W. *Cardiography*. London. Butterworths Medical Publications, 1948:1–95.

20 Barron SL. The development of the electrocardiograph in Great Britain. *Br Med J* 1950;i:720–5.

21 Goldhammer S, Scherf D. Elektrokardiographische Untersuchungen bei Kranken mit Angina pectoris ("ambulatorischer" Typus). *Z klin Med* 1932; 122:134–51.

22 Hollman A. The history of bundle branch block. *Med Hist* 1985;suppl 5:82–102.

23 Rosenbaum MB, Elizari MV, Lazzari JO. *The hemiblocks*. Oldsmar, Florida: Tampa Tracings, 1970.

24 Wolff L, Parkinson J, White PD. Bundle-branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia. *Am Heart J* 1930;5:685–99.

25 Cohn AE, Fraser FR. Paroxysmal tachycardia and the effect of stimulation of the vagus nerves by pressure. *Heart* 1913–14,5:93–105.

26 Hunter A, Papp C, Parkinson J. The syndrome of short P-R interval, apparent bundle branch block, and associated paroxysmal tachycardia. *Br Heart J* 1940;2:107–22.

27 Scherf D, Schott A. *Extrasystoles and allied arrhythmias*. London: William Heinemann Medical Books, 1973.

28 Lenègre J, Maurice P. De quelques résultats obtenus par la dérivation directe intracavitaire des courants électriques de l'oreillette et du ventricule droits. *Arch Mal Coeur* 1945;37–38:298–302.

29 Durrer D. Electrical aspects of human cardiac activity: a clinical electrophysiological approach to excitation and stimulation. *Cardiovasc Res* 1968;2:1–8.

30 Watson H, Emslie-Smith D, Lowe KG. The intracardiac electrogram of human atrioventricular conducting tissue. *Am Heart J* 1967;74:61–70.

31 Scherlag BJ, Lau SH, Helfant RH, Berkowitz WD, Stein E, Damato AN. Catheter techniques for recording His bundle activity in man. *Circulation* 1969;39:13–20.

32 Krikler DM, Goodwin JF, eds. *Cardiac arrhythmias: the modern electrophysiological approach*. London, Philadelphia, and Toronto: WB Saunders, 1975.

33 Meijler FL, Burchell HB, eds. *Professor Dirk Durrer. 35 years of cardiology in Amsterdam. A selection of papers and full bibliography*. Amsterdam: North-Holland Publishing Company, 1986.

34 Surawicz B. Prognosis of patients with chronic bundle branch block. *Circulation* 1979;60:40–2.

35 Lascault G, Guérot E, Péron M, Frank R, Fontaine G, Grosgogeat Y. Evolution à long-terme des troubles conductifs chez 73 patients appareilles pour un intervalle HV ⩾ 70 msec [Abstract]. *Arch Mal Coeur* 1986;79 1129.

36 Evans TR, Callowhill EA, Krikler DM. Clinical value of tests of sino-atrial function. *PACE* 1978;1:2–7.

37 Shaw DB, Kekwick CA. Potential candidates for pacemakers Survey of heart block and sinoatrial disorder (sick sinus syndrome). *Br Heart J* 1978;40:99–105.

38 Davies AB, Stephens MR, Davies AG. Carotid sinus hypersensitivity in patients presenting with syncope. *Br Heart J* 1979;42:583–6.

39 Gallagher JJ, Pritchett ELC, Sealy WC, Kasell J, Wallace AG. The pre-excitation syndromes. *Prog Cardiovasc Dis* 1978;20:285–327.

40 Spurrell RAJ, Krikler DM, Sowton E Concealed bypasses of the atrioventricular node in patients with

paroxysmal supraventricular tachycardia revealed by intracardiac electric stimulation and verapamil. *Am J Cardiol* 1974;33:590–5.

41 Schamroth L, Krikler DM, Garrett C. The immediate effects of intravenous verapamil in the treatment of cardiac arrhythmias. *Br Med J* 1972;1:660–2.

42 Rowland E, Evans T, Krikler D. Effects of nifedipine on atrioventricular conduction as compared with verapamil. Intracardiac electrophysiological study. *Br Heart J* 1979;42:124–7.

43 Wellens HJJ. The electrocardiogram 80 years after Einthoven. *J Am Coll Cardiol* 1986;7:484–91.

44 Spurrell RAJ, Krikler D, Sowton E. Two or more intra AV nodal pathways in association with either a James or Kent extranodal bypass in 3 patients with paroxysmal supraventricular tachycardia. *Br Heart J* 1973;35:113–22.

45 Webb SC, Krikler DM, Hendry WG, Adrian TE, Bloom SR. Electrophysiological actions of somatostatin on the atrioventricular junction in sinus rhythm and reentry tachycardia. *Br. Heart J* 1986; 56:236–41.

46 Ross DL, Johnson DC, Denniss AR, Cooper MJ, Richards DA, Uther JB. Curative surgery for atrioventricular junctional ("AV nodal") reentrant tachycardia. *J Am Coll Cardiol* 1985;6:1383–92.

47 Mendez C, Moe GK. Demonstrations of a dual AV nodal conduction system in the isolated rabbit heart. *Circ Res* 1966;19:378–93.

48 Schuilenberg RM, Durrer D. Further observations on the ventricular echo phenomenon elicited in the human heart. Is the atrium part of the echo pathway? *Circulation* 1972;45:629–38.

49 Wellens HJJ, Brugada P, Stevenson WG. Programmed electrical stimulation of the heart in patients with life-threatening ventricular arrhythmias: what is the significance of induced arrhythmias and what is the correct stimulation protocol? *Circulation* 1985;72:1–7.

50 Rahimtoola SH, Zipes DP, Akhtar M, *et al.* Consensus statement of the conference on the state of the art of electrophysiological testing in the diagnosis and treatment of patients with cardiac arrhythmias. *Circulation* (in press).

51 Skale BT, Miles WM, Heger JJ, Zipes DP, Prystowsky EN. Survivors of cardiac arrest: prevention of recurrence by drug therapy as predicted by electrophysiologic testing or electrocardiographic monitoring. *Am J Cardiol* 1986;57:113–9.

52 Anderson JL, Mason JW. Testing the efficacy of antiarrhythmic drugs. *N Engl J Med* 1986;315:391–3.

53 Rowland E, McKenna WJ, Sugrue D, Barclay R, Foale RA, Krikler DM. Ventricular tachycardia of left bundle branch block configuration in patients with isolated right ventricular dilatation. Clinical and electrophysiological features. *Br Heart J* 1984; 51:15–24.

54 Breithardt G, Schwarzmaier J, Borggrefe M, Haerten K, Seipel L. Prognostic significance of late ventricular potentials after acute myocardial infarction. *Eur Heart J* 1983;4:487–95.

55 Krikler DM. The development of the understanding of arrhythmias during the last 100 years. *Med Hist* 1985;suppl 5:77–81.

Br Heart J 1987;57:118–24

Increased cardiac electrical instability concomitant with pacing induced repolarisation abnormalities

PAOLO DELLA BELLA, SERGIO GRAZI, CARLO M CIPOLLA,
FRANCO FABBIOCCHI, ANDREA RIMONDINI, PAOLO SGANZERLA,
MAURIZIO D GUAZZI

From the Istituto di Cardiologia, Istituto di Ricerche Cardiovascolari "G Sisini", Centro Ricerche Cardiovascolari del Consiglio Nazionale delle-Ricerche, Fondazione "Italo Monzino", University of Milan, Italy

SUMMARY The relation between the occurrence of repolarisation abnormalities after right ventricular pacing and spontaneous arrhythmias was investigated in 16 patients in whom the sick sinus syndrome was suspected. All patients had normal QRS complexes and T waves in the electrocardiogram before pacing and required atrial stimulation and His bundle recording for diagnostic purposes. Patients were randomised into a study group or a control group. In the eight patients in the study group right ventricular pacing was performed for 12 hours, and was followed by inversion of the T wave in surface leads II, III, aVF, and V2–V5 and lengthening of the QTc interval. The frequency and complexity of ventricular arrhythmias increased after pacing in six patients who had ventricular extrasystoles in the baseline Holter recording. As the configuration of the T wave became normal the frequency of ventricular extrasystoles returned to baseline values. In the control group of eight patients ventricular pacing was not performed after the electrophysiological study and no changes were seen in T wave configuration and in the frequency of spontaneous arrhythmias.

These results suggest that the post-pacing repolarisation abnormalities reflect abnormal electrical properties of the ventricle and that in some cases they lead to increased electrical instability.

Abnormal ventricular depolarisation causes abnormal repolarisation which is manifested as T wave abnormalities. Transient abnormal repolarisation may be seen after the recovery of normal intraventricular conduction in patients with intermittent left bundle branch block,[1] temporary right ventricular pacing,[2 3] or intermittent ventricular preexcitation.[4 5] Rosenbaum *et al*[6] described the time course of T wave inversion after ventricular pacing and suggested that electrotonic modulation is responsible for the altered repolarisation that follows anomalous activation and that "accumulation" and "memory" of the new properties occur; these were said to account for the persistence of the repolarisation abnormalities.

The clinical significance of these post-pacing abnormalities of repolarisation is still controversial. A possible relation to myocardial ischaemia was proposed initially; however, these abnormalities also occur in the absence of coronary artery disease.[6] Electrical stimulation of the myocardium induces profound alterations of the electrical properties within the stimulated area,[7 8] and unequal recovery of the cardiac muscle increases vulnerability to arrhythmias.[9 10]

We have investigated whether the frequency of spontaneous arrhythmias changed during the repolarisation abnormalities caused by a period of right ventricular pacing.

Patients and methods

PATIENTS

We studied 16 patients (nine men and seven women;

Requests for reprints to Dr Paolo Della Bella, Istituto di Cardiologia, Via Bonfadini 214, 20138 Milan, Italy.

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mean age 57 years, range 43–68 years). They were randomised into a study or a control group (eight patients in each group). In all of them sinus node disease was suspected on the basis of repeated episodes of bradycardia and was the indication for an electrophysiological study. The electrocardiogram showed normal ventricular activation and repolarisation in all patients before the study. The axis of the QRS complex in the frontal plane lay between 0° and 90°. Coronary artery disease was excluded on the basis of history, clinical observation, resting and exercise electrocardiogram, and 24 hour Holter recording. Coronary angiography was performed in seven patients and was normal in all. In 10 patients (six in the study group and four in the control group) a 24 hour Holter recording showed ventricular extrasystoles of variable frequency, which were not symptomatic.

All patients gave informed written consent to the study including the invasive procedure and the stimulation period after the diagnostic electrophysiological study.

STIMULATION PROTOCOL

The diagnostic electrophysiological study, including the His bundle recording, was performed in both groups.

After the diagnostic procedures had been completed in the patients in the study group a bipolar or tripolar electrode catheter was advanced to the apex of the right ventricle to a position with a stimulation threshold of between 0·5 and 1·0 mA. A Medtronic programmable stimulator (model 5325) was used to deliver stimuli. Square wave pulses lasting 2 ms were given at twice diastolic threshold. The lowest possible pacing rate that ensured constant ventricular capture (between 70 and 90 beats/min) was used. Pacing was started at 8 pm and was continued for 12 hours in all patients. The lower cardiac rate during the night permits ventricular pacing at low rates. In the control group electrode catheters were withdrawn after the electrophysiological study, and electrocardiographic recordings and Holter monitorings were performed in the same way as in the study group.

ELECTROCARDIOGRAPHIC RECORDINGS

Electrocardiograms were recorded at a paper speed of 100 mm/s and high amplification (50 mm/mV) by means of an optically isolated polygraph (Hewlett Packard 4578 A). Electrocardiograms were obtained before and immediately at the end of the pacing period during the return of spontaneous sinus rhythm and 1, 2, 4, 6, and 12 hours after the end of pacing. Further electrocardiograms were recorded every 12 hours until the pacing induced repolarisation abnormalities disappeared. We measured the ventricular gradient in the frontal plane from the QRS and ST-T areas in leads I, II, III, and in single precordial leads (V3 and V4). The values given are the mean of five complexes. Planimetry of the tracings was performed with a Kontron computer. The area from the beginning of the QRS to the J point and that from the J point to the end of the T wave were regarded as the QRS and T areas. The mean electric axis and measured area of the ventricular gradient in the frontal plane were derived according to the rules described by Ashman and Byer.[11] Values for the QT interval were obtained by averaging the values of five beats on the three standard leads. We used Bazett's formula to correct the QT interval for heart rate.[12] Continuous 24 hour Holter recordings were obtained with an Avionics model 1445/B two channel recorder for (*a*) the day before pacing, (*b*) after the end of pacing, and (*c*) when the repolarisation abnormalities had unequivocally disappeared. Tape recordings were analysed by the same staff, using a Del Mar Avionics Trendsetter model DCG VII Dynamic Electrocardioscanner. The following data were measured for each patient: the total number of heart beats in the 24 hours, the highest and the lowest heart rates per minute, the frequency of ventricular extrasystoles in 24 hours, or of "complex" ventricular arrhythmias (couplets, runs of ventricular tachycardia). All recordings were started at 9 am. In some patients we also used direct electrocardiographic recording (Hewlett Packard 4700 A Pagewriter) to assess the hourly frequency of ventricular extrasystoles throughout the observation period. In all patients the results were similar to those obtained from Holter recording.

STATISTICAL ANALYSIS

The values of RR and QTc interval in control conditions and during various periods of observation were compared by Student's *t* test. A p value of <0.05 was regarded as significant. We used a Kontron computer, model Cardio 80, for statistical analysis.

Results

STUDY GROUP

Electrocardiographic measurements

The period of ventricular stimulation was followed by persistent repolarisation changes (fig 1). The following features were seen in all eight patients in the study group: (*a*) inversion of the T wave in leads II, III, and aVF, leading to a shift of the T wave vector leftwards and upwards; (*b*) significant leftward deviation of the ventricular gradient in the frontal plane; and (*c*) decrease of the measured area.

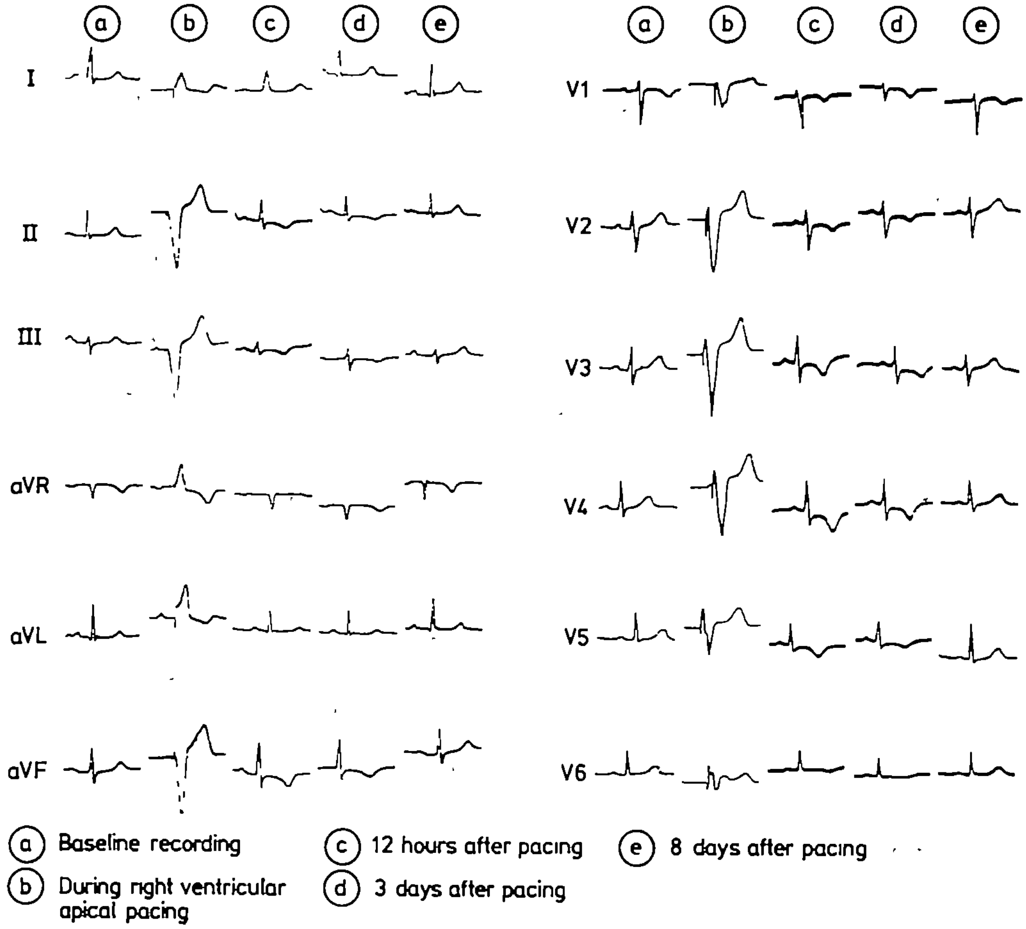

Fig 1 *Typical pattern of T wave changes on a 12 lead electrocardiogram before, during, and after right ventricular pacing in patient 1. The polarity of the inverted T wave is the same as that of the paced QRS. Repolarisation had returned to normal several days after the end of right ventricular pacing.*

The T wave from leads V2 to V5 was inverted in five patients, and in the remaining three it was flattened or reduced in amplitude in these leads. These changes were evident at the end of pacing and reached a maximum 2–12 hours after the end of pacing. Reversion of these abnormalities was slow, with restoration of the original values 5–22 days after the end of ventricular pacing (table 1). Figure 2 shows baseline and maximum values of the axis of the T wave and of the ventricular gradient. After stimulation all patients also showed a transient lengthening of the QTc interval which was greatest 4–24 hours (mean 12 hours) after ventricular pacing. The mean QTc interval increased from 409·8 to 446·0 ms ($p < 0.001$) in the absence of significant variations in the RR interval. The QTc interval values returned to their original values within 48 hours in all patients (table 2).

Table 1 *Time at which T wave inversion was greatest and at which the repolarisation changes returned to normal after right ventricular pacing*

Patient No	*Maximal T inversion (h)*	*Normal at (days)*
1	4	22
2	6	8
3	7	5
4	6	5
5	8	8
6	3	6
7	12	5
8	2	10

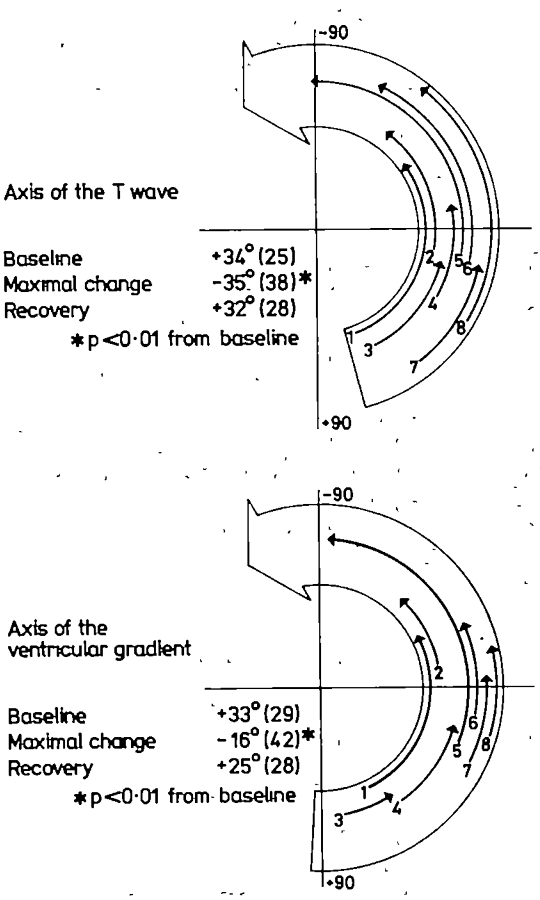

Fig 2 *Range of T wave axes and ventricular gradient distribution in patients in baseline conditions and at maximal shift after ventricular pacing. Mean (SD) values are shown.*

Holter recordings (table 3)

In each patient the total number of heart beats during the 24 hours was the same in all recordings, suggesting that the mean heart rate remained constant. The values for the highest and lowest heart rates in both early and late post-pacing recordings resembled those in the baseline recording. Patients 4 and 7, in whom no arrhythmias were seen in the baseline recording, had no spontaneous arrhythmias in the earlier (first 24 hours) and in the late (after disappearance of the repolarisation abnormalities) post-pacing Holter monitoring. In patients 1, 2, 3, 5, 6, and 8, however, who had premature ventricular beats before pacing, there was a remarkable increase in the frequency of these arrhythmias in the 24 hours after pacing. Several complex ventricular arrhythmias were seen. In case 3 ventricular extrasystoles of two different configurations and two couplets were present in the baseline Holter recording, and soon after the end of pacing we saw ventricular extrasystoles with three distinct configurations and several short episodes (3 to 4 beats) of ventricular tachycardia. Tachycardia was not detectable in the third Holter recording. In patient 6, who presented with single uniform ventricular extrasystoles in the baseline study, there were couplets and two short runs of ventricular tachycardia in the early post-pacing recording. These arrhythmias were not present in the later recording.

Figure 3 shows the strict relation between changes in repolarisation (ventricular gradient, QTc value) after pacing and the frequency of ventricular extrasystoles in patient 1. Repolarisation changes were most pronounced 12–24 hours after pacing, at the same time as the frequency of spontaneous arrhythmias increased. The frequency of these arrhythmias decreased as the pacing induced repolarisation changes returned to normal. In patients 2 and 8 the number of ventricular extrasystoles greatly increased in the 24 hours immediately after pacing and returned toward the baseline values during the last recording.

CONTROL GROUP

Analysis of the electrocardiograms showed no

Table 2 *QTc and RR intervals (ms) in the study group*

	Baseline		*Maximal change*		*Recovery*	
Patient No	*QTc*	*RR*	*QTc*	*RR*	*QTc*	*RR*
1	428	770	475	750	419	1033
2	396	903	438	873	398	1030
3	406	907	430	770	395	917
4	407	886	432	830	408	820
5	431	687	481	653	435	800
6	388	973	422	847	395	1043
7	418	800	454	913	409	1183
8	405	787	436	687	397	720
Mean (SD)	409·8 (14·9)	839·1 (93·3)	446·0* (21·8)	790·3† (91·2)	407·0† (14·1)	944·5† (156·3)

*p < 0·001 from baseline values.
†Not statistically different from baseline values.

Table 3 *Holter data in the study group*

Patient No	*Heart rate (min/max)*			*Total beats/24 h*			*Extrasystoles/24 h*		
	A	*B*	*C*	*A*	*B*	*C*	*A*	*B*	*C*
1	55/105	57/105	54/110	104832	106272	108000	12738	30284	14165
2	47/92	45/90	44/96	89712	83376	91440	416	1285	375
3	54/100	58/105	60/105	102384	110304	101644	31	75*	40
4	64/120	60/118	58/122	111168	112320	114336	0	0	0
5	60/104	62/100	55/106	107815	105470	106209	205	1013	272
6	48/100	50/92	49/95	84258	86976	87984	17	949†	85
7	50/90	48/92	47/85	100368	101520	97632	0	0	0
8	61/121	63/115	60/120	120672	119808	115488	75	177	82

*Including 4 episodes of ventricular tachycardia (3–4 beats).
†Including 2 episodes of ventricular tachycardia (3 beats).
A, baseline recording; B, first 24 hours after pacing, C, recovery.

difference in the axis of the T wave, in the ventricular gradient, and QTc interval in the control group when we compared data collected before and after the electrophysiological study. Four patients had ventricular arrhythmias; but the frequency of spontaneous arrhythmias seen during Holter monitoring after the electrophysiological study did not change. In the four patients who did not have arrhythmias during the baseline study there were no spontaneous arrhythmias during the second and third recordings.

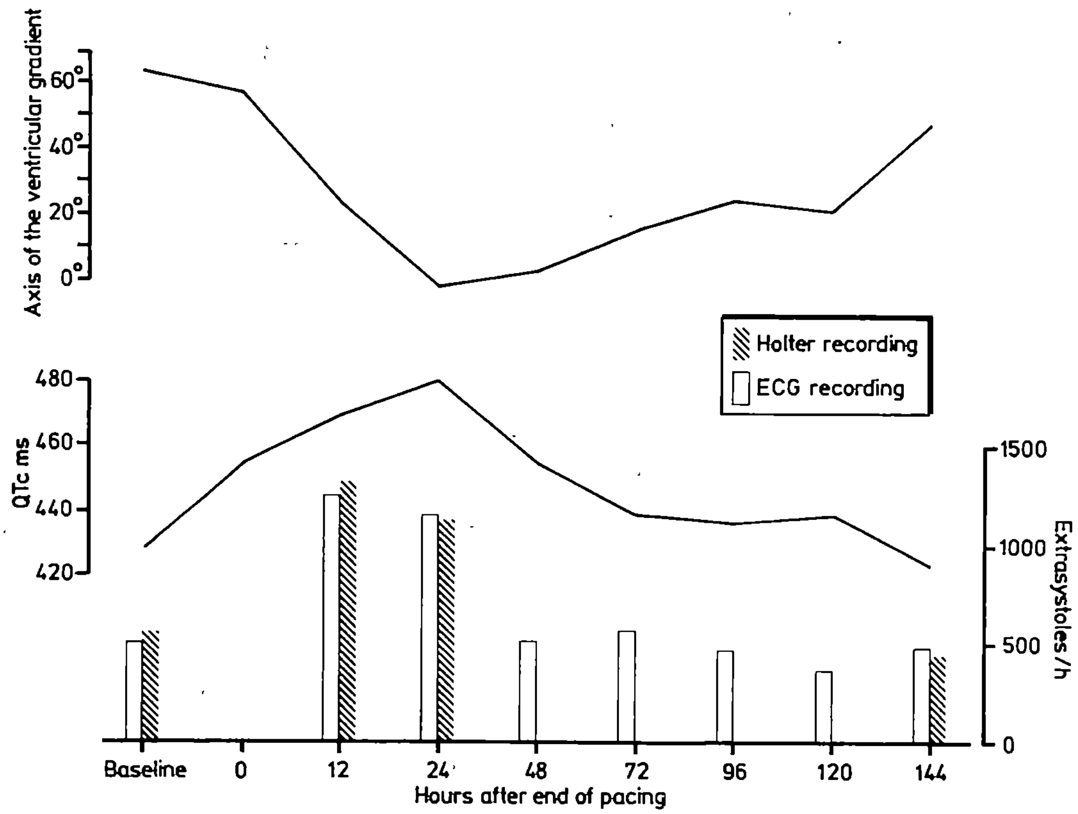

Fig 3 *Axis of the ventricular gradient, QTc interval, and arrhythmia frequency expressed as ventricular extrasystoles per hour in the baseline recordings and after right ventricular pacing in patient 1. The frequency of extrasystoles in the baseline recording and at 12, 24, and 144 hours (6th day) was obtained from Holter recordings. At other times data were obtained from direct electrocardiographic monitoring (see Methods).*

Discussion

The presence of changes in ventricular repolarisation and an increased frequency of spontaneous ventricular arrhythmias in the patients of the study group but not in the control group suggests that ventricular stimulation rather than other procedures was responsible for these changes.

REPOLARISATION ABNORMALITIES INDUCED BY VENTRICULAR PACING AND SPONTANEOUS ARRHYTHMIAS

Patients who had no arrhythmias in the baseline study did not show spontaneous arrhythmias when repolarisation abnormalities were induced by a 12 hour period of right ventricular pacing. In patients who presented with ventricular arrhythmias, however, we found that a 2–15 fold increase in ventricular arrhythmias and the presence of ventricular tachycardia were accompanied by the appearance of post-pacing repolarisation abnormalities. This, and the return to baseline values of the ventricular arrhythmias with recovery of normal repolarisation, virtually excluded spontaneous variability of ventricular ectopy.[13 14]

The strict temporal relation between repolarisation abnormalities and worsening of spontaneous arrhythmias suggests that spontaneous electrical instability was exacerbated by changes in the ventricular gradient and the lengthening of the QTc interval. In some patients these repolarisation abnormalities may reflect an increased electrical instability.

The basis for this effect could be an increase in the inequalities of recovery in different areas of the myocardium. In a series of experiments by Kuo *et al*[15] a previously "innocuous" premature stimulus could at a critical degree of dispersion of repolarisation trigger repetitive responses that eventually led to ventricular fibrillation. In that study changes in the T wave and prolongation of QTc interval were evident at the time of induction of ventricular fibrillation. Also repetitive responses could be induced when a critical degree of dispersion of repolarisation was reached, even when spontaneous arrhythmias did not occur during the control period. These data suggest that electrical instability may be caused by repolarisation abnormalities even in the absence of spontaneous arrhythmias before the repolarisation abnormalities were induced.

The reported experimental data may be clinically relevant to our study. Our patients without arrhythmias in the baseline recording remained free from arrhythmias after pacing induced changes in repolarisation, probably because the degree of dispersion of repolarisation that was achieved was not sufficient to induce spontaneous arrhythmias. In contrast the increased electrical instability that accompanied the post-pacing repolarisation abnormalities in patients with pre-existing spontaneous ventricular arrhythmias may have increased the frequency of single ectopic complexes and the spontaneous occurrence of the repetitive arrhythmias.

Torsade de pointe has been described at the end of ventricular pacing (patient 1 in reference 16). The electrocardiogram of this patient showed inversion of the T wave in leads II, III, aVF, and in the precordial leads and no prolongation of the QT interval. These findings suggested a possible role of repolarisation abnormalities and increased electrical instability in the genesis of the arrhythmia.

POSSIBLE MECHANISMS OF REPOLARISATION ABNORMALITIES

In all patients in this study right ventricular pacing was followed by a shift toward the left and upwards of the T wave vector and of the ventricular gradient in the frontal plane. Our data show that the repolarisation sequence has shifted. Repolarisation is proceeding in the opposite direction to the basal state. This may be caused by a lengthening of action potential in the apical regions as a result of right ventricular apical pacing. Repolarisation proceeds from the epicardium to the endocardium[17 18]; a positive T wave is related to the shorter refractory period and shorter monophasic action potential in the epicardial than in the endocardial layers[19 20]; the inversion of the T wave in the precordial leads after ventricular pacing may reflect a relative lengthening of the action potential in the epicardium (or in the right surface of the interventricular septum) compared with the endocardial layers of the left ventricle.

The time course of changes and recovery to baseline values was similar for both ventricular gradient and QTc interval, suggesting that the two events may share a common mechanism. The lengthening of the QT interval could be related to the degree of dispersion of repolarisation caused by prolongation of action potential in the stimulation area.

T WAVE MEMORY?

It has been suggested that the persistence of the observed repolarisation abnormalities beyond the period of ventricular pacing is related to the possible effects of electrotonic currents.[6] This view, however, has been criticised,[21 22] because electrotonic currents, which are passive phenomena, should only affect the repolarisation sequence associated with a given depolarisation. Therefore, after the recovery of normal intraventricular activation a repolarisation sequence similar to the original should occur.

Cohen *et al* proposed a different explanation for the development and persistence of the repolarisation abnormalities.[23] They suggested that the continuous electrical activity of the heart itself is responsible for the genesis of an electrical gradient throughout the ventricles and that metabolic factors are involved in the maintenance of inequalities in repolarisation. The time course of recovery to normal repolarisation of our study suggests the possibility that metabolic factors can play a role in the persistence of the T wave changes.

We found that the repolarisation abnormalities that occur after ventricular pacing, which previously have not be regarded as clinically relevant, may be clinically important. Inversion of the T wave after ventricular pacing was accompanied by an increased electrical instability, which was manifested by a higher frequency of spontaneous ventricular arrhythmias. Patients in whom prolonged ventricular pacing is suddenly stopped may demonstrate increased electrical instability in the early phase after the end of pacing. Patients with pre-existing ventricular arrhythmias are particularly susceptible to such instability.

References

1 Denes P, Pick A, Miller RH, Pietras RJ, Rosen KM. A characteristic precordial repolarization abnormality with intermittent left bundle branch block. *Ann Intern Med* 1978;89:55–7.

2 Gould L, Venkataraman K, Goswami MK, Gomprecht RF. Pacemaker-induced electrocardiographic changes simulating myocardial infarction. *Chest* 1973,63:829–33.

3 Chatterjee K, Harris A, Davies G, Leatham A. Electrocardiographic changes subsequent to artificial ventricular depolarisation. *Br Heart J* 1969;31:770–9.

4 Nicolai P. Le syndrome de Wolff-Parkinson-White. In: *Les cahiers de médicographie*. Suresnes: Servier, 1966:35.

5 Nicolai P, Medvedowsky JL, Delaage M, Barnay C, Blache E, Pisapia A. Wolff-Parkinson-White syndrome: T wave abnormalities during normal pathways conduction. *J Electrocardiol* 1981;14:295–300.

6 Rosenbaum MB, Blanco HH, Elizari MV, Lazzari JO, Davidenko JM. Electrotonic modulation of the T wave and cardiac memory. *Am J Cardiol* 1982; 50:213–22.

7 Kuo CS, Amlie JP, Munakata K, Reddy CP, Surawicz B. Dispersion of monophasic action potential durations and activation times during atrial pacing, ventricular pacing, and ventricular premature stimulation in canine ventricles. *Cardiovasc Res* 1983; 17:152–61.

8 Avitall B, Levine HJ, Naimi S, Donahue RP, Pauker SG, Adam D. Local effects of electrical and mechanical stimulation on the recovery properties of the canine ventricle. *Am J Cardiol* 1982;50:263–70.

9 Urie P, Burgess MJ, Lux RL, Wyatt RF, Abildskov JA. The electrocardiographic recognition of cardiac states at high risk of ventricular arrhythmias. *Circ Res* 1978;42:350–8.

10 Burgess MJ. Relation of ventricular repolarization to electrocardiographic T wave-form and arrhythmia vulnerability. *Am J Physiol* 1979;236:H391–402.

11 Ashman R, Byer E. The normal human ventricular gradient. I. Factors which affect its direction and its relation to the mean QRS axis. *Am Heart J* 1943;25:16–35.

12 Bazett HC. An analysis of the time relations of electrocardiogram. *Heart* 1920;7:353–70.

13 Winkle RA. Antiarrhythmic drug effect mimicked by spontaneous variability of ventricular ectopy. *Circulation* 1978;57:1116–20.

14 Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB. Limitations of routine long term electrocardiographic monitoring to assess ventricular ectopic frequency. *Circulation* 1978;58:408–14.

15 Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanisms of ventricular arrhythmia dependent on the dispersion of action potential durations. *Circulation* 1983;67:1356–67.

16 Steinbrecher UP, Fitchett DH. Torsade de pointes. A cause of syncope with atrioventricular block. *Arch Intern Med* 1980;140:1223–6.

17 Spach M, Barr RC. Ventricular intramural and epicardial potential distributions during ventricular activation and repolarisation in the intact heart. *Circ Res* 1975;37:243–57.

18 Moore EN, Preston JB, Moe GK. Durations of transmembrane action potentials and functional refractory periods of canine false tendon and ventricular myocardium. *Circ Res* 1965;17:259–73.

19 Reynolds EW, Vander Ark CR. An experimental study of the origin of T waves based on determinations of effect refractory period from epicardial and endocardial aspects of the ventricle. *Circ Res* 1959; 8:943–9.

20 Higuchi T, Nakaja Y. T wave polarity related to the repolarization process of epicardial and endocardial ventricular surfaces. *Am Heart J* 1984;108:290–5.

21 Hoffman BF. Electrotonic modulation of the T wave. *Am J Cardiol* 1982;50:361–2.

22 Surawicz B. Transient T wave abnormalities in intermittent bundle branch block. *Am J Cardiol* 1982;50:363–4.

23 Cohen I, Giles W, Noble D. Cellular basis for the T wave of the electrocardiogram. *Nature* 1976;262: 657–61.

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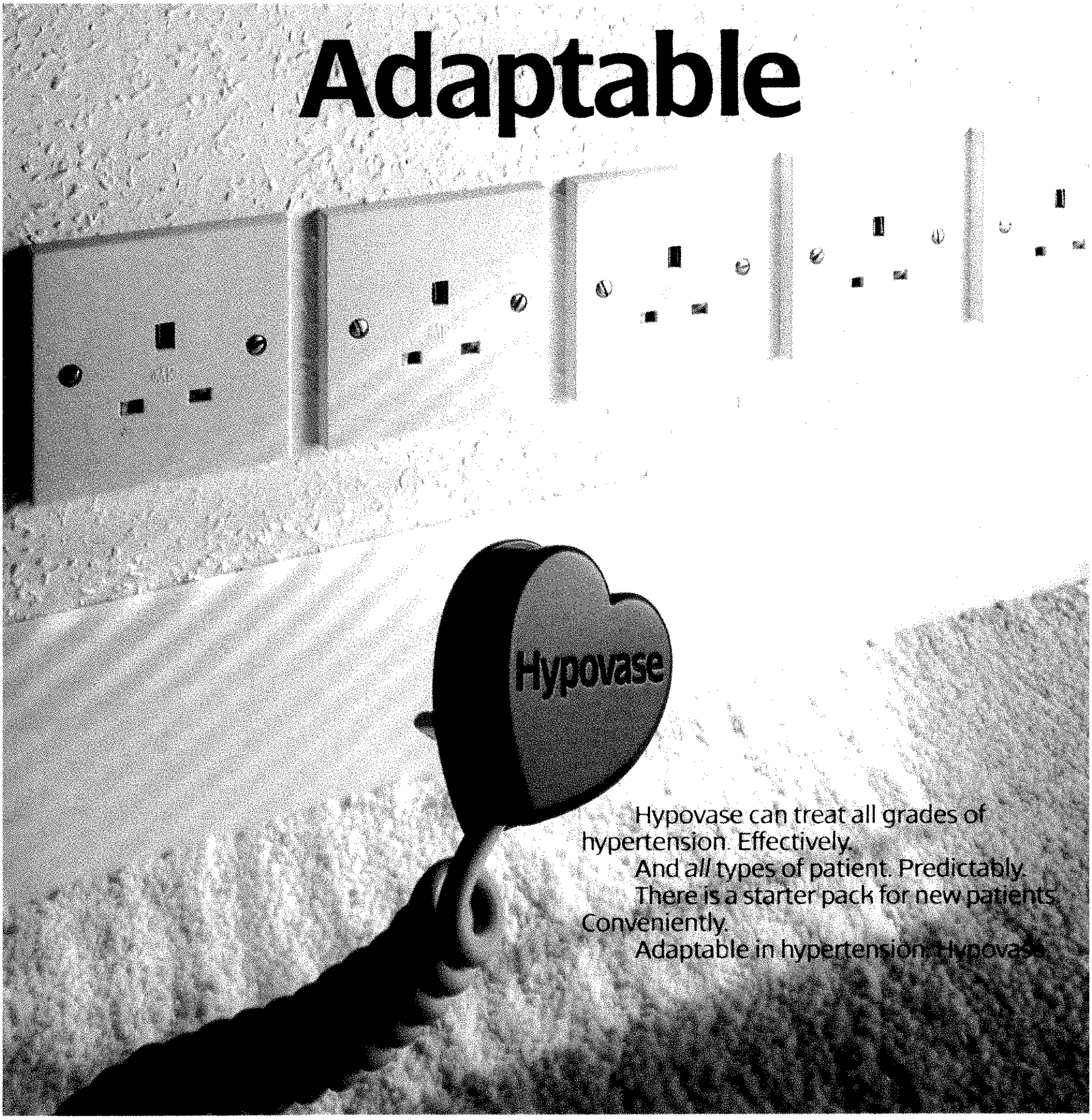
Use Control of mild to moderate hypertension. 'Inderal' LA and Half-'Inderal' LA are also indicated for angina, anxiety, essential tremor, thyrotoxicosis and prophylaxis of migraine. **Dosage and administration Hypertension** One capsule daily of 'Inderex' or one capsule daily of 'Inderal' LA increasing by increments of one capsule of Half-'Inderal' LA if required. **Other indications** One capsule daily of Half-'Inderal' LA increasing to the equivalent of 3 capsules daily if required. **Elderly patients** Start with one capsule daily Half-'Inderal' LA. **Contraindications** Heart block; bronchospasm; after prolonged fasting; and in metabolic acidosis. Additionally with 'Inderex': hypokalaemia (especially in patients already potassium depleted); hyperuricaemia. Rare reports of rashes, necrotising vasculitis, acute pancreatitis, blood dyscrasias and aggravation of pre-existing myopia. **Product licence numbers and basic NHS cost** (28-day calendar pack) 'Inderal' LA (29/0128) £6.66; Half-'Inderal' LA (29/0173) £4.48; 'Inderex' (29/0157) £7.44. 'Inderal' LA, Half-'Inderal' LA and 'Inderex' are trademarks. Further information is available from: ICI Pharmaceuticals (UK), Alderley House, Alderley Park, Macclesfield, Cheshire SK10 4TF.

thiazides. **Precautions** Untreated cardiac failure; bradycardia. Treatment modifies tachycardia of hypoglycaemia. Transference from, or discontinuance of, clonidine. Prescription of Class I antidysrhythmic agents. Co-administration with verapamil. Anaesthesia. Pregnancy. Cessation of beta-blocker therapy should be gradual in patients with ischaemic heart disease. Additionally with 'Inderex': diabetes; hepatic cirrhosis with ascites; and co-administration of digitalis or lithium containing preparations. **Side effects** Cold extremities, nausea, insomnia, lassitude and diarrhoea are usually transient. Isolated cases of paraesthesia of the hands. Rashes and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Prescribing Information in Hypertension: Indications Hypovase is indicated in the treatment of hypertension of varied aetiology and all grades of severity. It can be used alone or in conjunction with other anti-hypertensive drugs such as a beta-blocker or a thiazide diuretic. **Contra-indications** Sensitivity to Hypovase. **Precautions** A small percentage of patients may react more rapidly and to a greater extent than the majority. In some cases this has led to sudden loss of consciousness generally lasting a few minutes. Subsequent treatment may be satisfactory. **WARNINGS: Use during pregnancy.** Although no teratogenic effects were seen in animal testing, the safety of Hypovase use during pregnancy or during lactation has not yet been established. Accordingly, it should be used, during these times only when in the opinion of the physician, potential benefit outweighs potential risk. **Use for children** Hypovase is not recommended for the treatment of children under the age of twelve years since safe conditions for its use have not been established. **Side-effects** Dizziness, drowsiness and lack of energy are the most common. **Dosage** Starting dose 0.5mg two or three hours before retiring; thereafter up to 20mg daily in divided doses. **Basic NHS Cost** 0.5mg tablet (PL57/0149) pack of 100, £4.08; 1mg tablet (PL57/0106) pack of 100, £5.25; 2mg tablet (PL57/0107) pack of 100, £6.98; 5mg tablet (PL57/0108) pack of 100, £15.58. Also available is a b.d Starter Pack for hypertension only containing 8 x 0.5mg and 32 x 1mg Hypovase tablets £2.70. Further information on request. Pfizer Ltd., Sandwich, Kent. *Trade Mark.

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Br Heart J 1987;57:125–32

Factors influencing survival and mode of death in severe chronic ischaemic cardiac failure

DAVID R GLOVER, WILLIAM A LITTLER

From the Department of Cardiovascular Medicine, University of Birmingham, East Birmingham Hospital, Birmingham

SUMMARY An evaluation of factors which may influence survival and mode of death was conducted over a three year period in a consecutive series of 50 patients with severe chronic ischaemic cardiac failure for more than three months. At the initial assessment all patients were already receiving intensive medical treatment. During follow up four patients successfully underwent cardiac surgery and medical treatment was modified in most patients, with four patients receiving antiarrhythmic drugs. Twenty six patients died: 17 suddenly within one hour of onset of symptoms and nine of progressive cardiac failure. The mortality by one year was 26% and by two years it was 62%. Comparison of those who survived with those who died within one year of follow up showed that a very low left ventricular ejection fraction, severe ventricular arrhythmias, the presence of gallop rhythm, and New York Heart Association class IV were the variables that predicted mortality. By two years left ventricular ejection fraction, ventricular arrhythmias, and pulmonary capillary wedge pressure were the variables that were significantly different in survivors and patients who died. No differences were found in any of the recorded variables between those who died suddenly and those who did not.

Thus in patients with chronic ischaemic cardiac failure determination of the left ventricular ejection fraction and the severity of ventricular arrhythmia on the ambulatory electrocardiogram are the best ways to predict prognosis. The presence of gallop rhythm and New York Heart Association class IV status predict early death.

Severe chronic cardiac failure occurring as a consequence of ischaemic heart disease is common. Many studies in the United States have documented the course of the disease[1-3] and have described certain indicators of outcome.[4-6] The Framingham Study emphasised that the prognosis was little better than for cancer in general.[7] Surprisingly there is no major United Kingdom contribution to published reports on this topic.

In the past decade there has been considerable interest in new drug treatments for severe cardiac failure, especially vasodilators[3 8 9] and inotropes,[10-12] with considerable attention being paid to the influence of these drugs on haemodynamic variables and exercise tolerance. Despite these newer drugs the mortality from the syndrome remains high and the prognosis remains poor. An editorial by Wilson reviewed the subject and advocated optimisation of medical treatment by the physician, and education of the patient's family in the recognition of the signs of sustained ventricular tachycardia and training in cardiopulmonary resuscitation because at least half of such patients die suddenly.[13]

We describe our experience gained over three years at a major referral centre for cardiology patients, describe the course of the disease, and identify factors that influence survival and mode of death in patients with chronic ischaemic cardiac failure.

Patients and methods

INCLUSION CRITERIA

Patients were recruited from routine outpatient practice. Fifty consecutive patients were entered

Requests for reprints to Dr David R Glover, Medical Department, Merck Sharp and Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

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according to the following criteria: *(a)* age <70 years; *(b)* proven diagnosis of ischaemic heart disease, either documented previous myocardial infarction and/or presence of significant (>50%) narrowing of one or more major coronary arteries demonstrated at coronary angiography; *(c)* left ventricular failure of more than three months' duration, characterised by any or several of the following—dyspnoea and/or fatigue or exertion, paroxysmal nocturnal dyspnoea, peripheral oedema, gallop rhythm, pulmonary congestion, and documented by reduced left ventricular ejection fraction measured either by cineangiography or by radionuclide angiography or by M mode echocardiography and requiring treatment with diuretics with or without digoxin and/or drugs with vasodilator activity.

Patients were specifically excluded if there was evidence of significant valvar heart disease or chronic obstructive airways disease. Inpatients were not included but were identified and included in the study if they were eligible when they attended as outpatients.

CLINICAL ASSESSMENT AND FOLLOW UP

The initial clinical assessment included a review of all previous investigations. The date of initiation of diuretic treatment was taken as the date of onset of left ventricular failure. All current medication at the time of assessment was noted, and further investigations to confirm and elucidate the diagnosis of left ventricular failure as a consequence of coronary artery disease were performed within six weeks. The New York Heart Association functional classification was assessed.

All patients were followed up regularly and medical treatment was changed or operation performed when appropriate. Details of deaths were obtained from hospital inpatient case records, general practitioners' records, and relatives' accounts. The date, cause, and mode of death was ascertained; for the purpose of this study death was defined as sudden if it occurred within one hour of onset of symptoms and/or was unexpected. The minimum follow up for survivors was 15 months.

STATISTICAL ANALYSIS

Survivors and deaths were compared at one and two years by an unpaired Student's t test or a χ^2 test as appropriate. Sudden and non-sudden deaths were compared by the same criteria. A p value of $<0{\cdot}05$ was taken as significant.

Results

PATIENT CHARACTERISTICS

Age and sex

There were 40 (80%) men and 10 (20%) women (mean (SD) age 56·9 (6·7) years, range 39–70).

Medical history

The mean (SD) duration of left ventricular failure was 16·7 (13·6) months (range 3–65 months). Ischaemic heart disease was confirmed by documented previous myocardial infarction in 43 (86%) patients and by coronary angiography in the remaining seven (14%) patients who had not had a myocardial infarction. The number of myocardial infarctions was zero in seven patients, one in 21 patients, two in 13 patients, three in eight patients, and >3 in one patient. Coronary angiography was performed in 42 patients: single vessel disease was found in three patients, double vessel disease in two patients, and triple vessel disease in 37 patients. Eleven (22%) patients had a history of hypertension (blood pressure >160/95 mm Hg) that required treatment. None of the patients was hypertensive at assessment. Seven (14%) patients had diabetes mellitus. Previous pulmonary embolism was documented in four (8%) patients. Two patients had previously undergone coronary artery bypass surgery, and a further two patients had had peripheral vascular surgery.

Symptoms and physical signs

All 50 patients complained of dyspnoea and/or fatigue on exertion. Forty (80%) patients had angina pectoris and seven (14%) patients had intermittent claudication. Sinus rhythm was present in 45 (90%) patients and atrial fibrillation was present in the remaining five (10%) patients.

An added heart sound, either third, fourth or both, was present in 35 (70%) patients. A murmur characteristic of mild mitral regurgitation was present in 15 (30%) patients. Auscultation of the chest was clear in 25 (50%) patients and revealed basal rales in 21 (42%) patients and rales halfway up both lung fields in two (4%) patients. Peripheral oedema confined to the ankle area was present in five (10%) patients.

Other characteristics

Forty seven (94%) patients smoked cigarettes or were recent ex-smokers; only four (8%) patients were obese (>120% of desirable body weight).

Existing medication

Digitalis preparations were being taken by 44 (88%) patients: 37 patients were taking digoxin (mean (SD) daily dose 0·23 (0·05) mg) and seven patients were taking medigoxin (mean daily dose 0·17 (0·08) mg). Diuretics were being taken by all 50 patients: 47 patients were taking frusemide (mean daily dose 121 (139) mg, range 40–1000 mg) and three were taking bumetanide (mean daily dose 1·5 (0·5) mg). An additional potassium sparing diuretic was being taken by 28 (56%) patients: 25 patients were taking spironolactone (mean (SD) daily dose 106 (33) mg) and three patients were taking amiloride 10 mg daily. All 50 patients were normokalaemic (serum potassium 3·4–5·3 mmol/l) at the time of assessment. Vasodilator drugs were being taken by 28 (56%) patients: 21 (42%) patients were on isosorbide dinitrate (mean (SD) daily dose 46 (33) mg, range 20–90 mg). Eleven patients were taking other drugs with vasodilator activity; in eight patients it was a calcium antagonist (either nifedipine or verapamil); four of these patients were also taking nitrates. The remaining three patients were taking hydralazine (two patients) or prazosin (one patient).

Two patients were on antiarrhythmic drugs (amiodarone 200 mg daily). Other drugs included warfarin, six patients; oral hypoglycaemic drugs, four patients; thyroxine, one patient; and insulin, one patient.

Functional classification

The New York Heart Association functional classification based on symptoms was: class II, three patients (three male, 0 female); class III, 37 patients (30 male, seven female); class IV, 10 patients (seven male, three female).

ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND OTHER INVESTIGATIONS

Electrocardiogram

The standard 12 lead electrocardiogram was normal in only three patients. An old anterior myocardial infarction was the commonest abnormality, occurring in 37 (74%) patients; in 12 of these patients there was also evidence of old inferior myocardial infarction. Two patients had evidence of old inferior myocardial infarction alone. The remaining eight patients had one of a variety of abnormalities: complete left bundle branch block, left ventricular hypertrophy, T wave inversion, and atrial fibrillation.

Chest x ray

The cardiothoracic ratio was increased (≥0 50) in 45 (90%) patients. The mean (SD) cardiothoracic ratio was 0·55 (0·06). Twelve patients (24%) had normal lung fields, with the remaining 38 (76%) patients having evidence of passive pulmonary congestion of a mild to moderate degree. No patient had frank pulmonary oedema at the time of assessment.

Left ventricular function

The left ventricular ejection fraction was measured in 46 (92%) patients. Cineangiography was performed in 41 patients and equlibrium radionuclide angiography (with in vivo labelling of the patient's own red blood cells with technetium-99m) in 23 patients. The four patients who did not have the left ventricular ejection fraction measured all had M mode echocardiography performed; the left ventricular and diastolic diameter was >6·0 cm in all four patients and the mean (SD) fractional shortening was 0·019 (0·08). The mean (SD) cineangiographic left ventricular ejection fraction was 0·28 (0·14) and the mean (SD) radionuclide left ventricular ejection fraction was 0·26 (0 09). Echocardiographic fractional shortening was measured in 43 patients (mean (SD) 0 18 (0·07). Pulmonary capillary wedge pressure was measured in 40 patients (mean (SD) 21·3 (7·8) mm Hg.

Exercise capacity

Maximum exercise capacity was measured in 29 patients. A bicycle ergometer was used with a protocol which began at a workload of 20 W for two minutes and increased by 10 W per minute thereafter. The mean (SD) maximum workload achieved was 76·0 (25·7) W.

Ambulatory electrocardiogram

Ambulatory 24 hour electrocardiograph recording was performed in 27 (54%) patients. There was no selection process. The mean left ventricular ejection fraction in these patients was 0·26—that is, the same as in the group overall. The severity of ventricular arrhythmias was scored by the Lown classification.[14] All patients had evidence of ventricular arrhythmias. The classification of patients was as follows: grade 0, no patients; grade 1, 10 patients; grade 2, seven patients; grade 3, one patient; grade 4A, two patients; grade 4B, five patients; and grade 5, two patients.

FOLLOW UP DETAILS

Status: dead or alive

Twenty six (52%) patients died during follow up. The mean (SD) follow up from assessment was 17·7 (10·8) months; follow up for those who died was 11·3 (10·2) months and for survivors it was 24·7 (6·3) months. Figures 1 and 2 show life table analyses from assessment and from onset of left ventricular failure. Death was sudden in 17 patients and due to progressive cardiac failure in nine patients. No deaths were attributable to non-cardiac causes.

Tables 1, 2, and 3 show the demographic and clinical details, treatment, and assessment of cardiac function in survivors and patients who died. Death within one year was most likely to occur in those patients with the lowest left ventricular ejection fraction, the highest Lown grade for 24 hour ambulatory electrocardiographic recording, in the presence of a gallop rhythm, and in those classified as New York Heart Association functional class IV. Death within

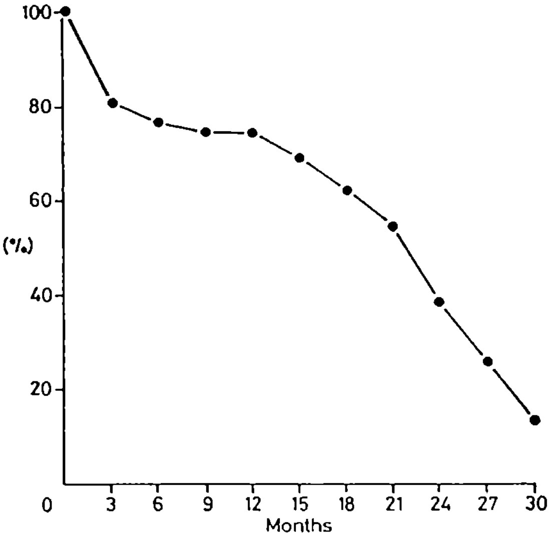

Fig 1 *Life table analysis: from assessment of left ventricular failure.*

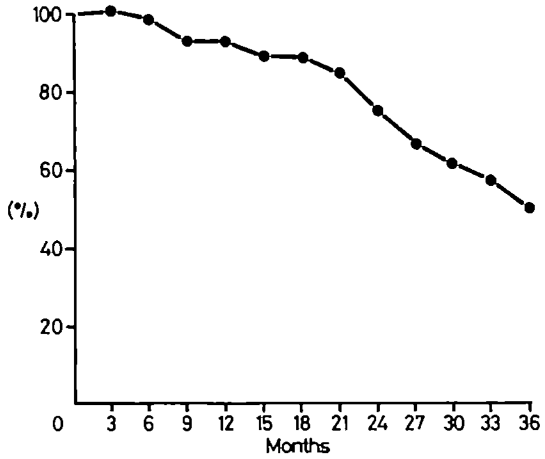

Fig 2 *Life table analysis: from onset of left ventricular failure.*

two years was predicted by left ventricular ejection fraction, Lown grade, and pulmonary capillary wedge pressure.

None of the other variables influenced survival. Table 4 shows a comparison of sudden and non-

Table 1 *Survivors versus deaths at one and two years' follow up: clinical details*

	By 12 months			*By 24 months*		
	Survivors (n = 37)	*Deaths (n = 13)*	*Significance*	*Survivors (n = 15)*	*Deaths (n = 24)*	*Significance*
Age (years) (mean (SD))	56·8 (6·95)	57·2 (6·13)	NS	54·7 (7·60)	57·8 (6·01)	NS
Sex (male:female)	28:9	12:1	NS	10:5	22:2	$p < 0·05$
Duration of LVF (months) (mean (SD))	17·1 (14·62)	15·5 (10·78)	NS	21·7 (14·22)	14·2 (9·80)	NS
NYHA class:						
II	3	0		1	2	
III	30	7	$p < 0·01$	13	15	NS
IV	4	6		1	7	
Gallop rhythm (%)	23 (62%)	12 (92%)	$p < 0·05$	10 (67%)	16 (67%)	NS
Mitral regurgitation (%)	12 (23%)	3 (23%)	NS	4 (27%)	7 (29%)	NS
Previous MIs						
0	4	3		0	3	
1	16	5		8	9	
2	11	2	NS	6	4	NS
>2	6	3		1	7	

LVF, left ventricular function, NYHA, New York Heart Association, MIs, myocardial infarctions.

Table 2 *Survivors versus deaths at one and two years' follow up: medication*

	By 12 months			*By 24 months*		
	Survivors (n = 37)	*Deaths (n = 13)*	*Significance*	*Survivors (n = 15)*	*Deaths (n = 24)*	*Significance*
Frusemide (mg) (mean (SD))	122·4 (160·59)	116·9 (52·82)	NS	82·9 (36·67)	158·2 (195·76)	NS
Digoxin:						
Dose (mg) (mean (SD))	0·23 (0·44)	0·21 (0·063)	NS	0·22 (0·055)	0·22 (0·055)	NS
(n (%))	33 (89%)	11 (85%)		13 (87%)	20 (83%)	NS
Potassium sparing diuretics (n (%))	20 (54%)	8 (62%)	NS	7 (47%)	13 (54%)	NS
Vasodilators (n (%))	20 (54%)	8 (62%)	NS	8 (53%)	13 (54%)	NS

Table 3 *Survivors versus deaths at one and two years' follow up: cardiac assessment*

	By 12 months			*By 24 months*		
Variable	*Survivors (n = 37)*	*Deaths (n = 13)*	*Significance*	*Survivors (n = 15)*	*Deaths (n = 24)*	*Significance*
PCWP (mm Hg) (n)	20 9 (7·72) (31)	24 0 (8·60) (10)	NS	18·0 (7·04) (11)	24·3 (8·23) (19)	p < 0 05
LV cine EF (mean (SD)) (n)	0 31 (0 134) (31)	0·18 (0·087) (10)	p < 0 01	0 41 (0·108) (11)	0 22 (0 086) (7)	p < 0 001
RNLVEF (mean (SD) (n)	0 26 (0 073) (20)	0 22 (0 113) (3)	NS	0·29 (0 081) (9)	0 22 (0 086) (7)	NS
Cardiothoracic ratio (mean (SD) (n)	0·54 (0 061) (37)	0 57 (0 046) (13)	NS	0 55 (0 078) (15)	0 56 (0 045) (24)	NS
Echo FS (mean (SD)) (n)	0·19 (0 068) (34)	0 14 (0 071) (9)	NS	0 19 (0 081) (15)	0 16 (0 064) (18)	NS
Lown grade						
1	9	1	p < 0 02	7	3	p < 0 02
2	7	0		7	0	
3	0	1		0	1	
4A	1	1		0	2	
4B	2	3		1	4	
5	2	0		1	1	
Exercise capacity (W) (mean (SD)) (n)	78 8 (25 22) (25)	62·0 (25·88) (5)	NS	80·0 (76 46) (9)	71 8 (24 01) (11)	NS

PCWP, pulmonary capillary wedge pressure; LV cine EF, left ventricular ejection fraction measured by cineangiography; RNLVEF, radionuclide left ventricular ejection fraction; Echo FS, fractional shortening measured by echocardiography.

Table 4 *Sudden versus non-sudden deaths*

Variable	*Sudden deaths (n = 17)*	*Non-sudden deaths (n = 9)*	*Significance*
Age (years)	56 6 (7 0)	58 8 (7·3)	NS
Sex (M:F)	17:0	7:2	NS
Duration of left ventricular failure (mnth)	13·2 (8·7) (17)	19 4 (15 4) (9)	NS
Previous MIs	1 71 (1·53 (17)	1·56 (1 01) (19)	NS
Gallop rhythm	9	8	NS
Mitral regurgitation (n)	5	3	NS
NYHA class (n) II	2	0	
III	12	5	NS
IV	3	4	
Medication:			
Frusemide (mg) (mean (SD))	155 (228)	154 (67)	NS
Digoxin (n)	14	7	NS
K^+ supplements (n)	9	5	NS
Vasodilators (n)	8	6	NS
Pulmonary capillary wedge pressure (mm Hg)	23·3 (7 1) (13)	25·0 (10 5) (7)	NS
LV cine EF (mean (SD)) (n)	21·9 (7 6) (13)	16 9 (8 7) (6)	NS
RNLVEF	23 0 (9 4) (4)	20 7 (9·1) (3)	NS
Lown grade	3 36 (1 63) (7)	3·38 (1·80) (4)	NS
Cardiothoracic ratio	0 56 (0·04) (17)	0 57 (0 05) (9)	NS
Echo fractional shortening	0 15 (0·06) (13)	0·16 (0·07) (7)	NS
Maximum exercise capacity (W)	81 4 (21 2) (7)	55·0 (20 8) (4)	NS

Results are expressed as mean (SD) (n).
RNLVEF, radionuclide left ventricular ejection fraction, ECG, 12 lead electrocardiogram; LV cine EF, left ventricular ejection fraction.

sudden deaths. No differences were detected for any of the recorded variables between sudden and non-sudden deaths.

Alteration in treatment and surgical referral

After the initial assessments only three (6%) patients continued on unchanged medication because this was judged to be optimal. Five (10%) patients died before any necessary alterations in treatment could be effected. Twenty two (44%) patients entered a six month trial of oral prenalterol versus placebo[15]; 11 patients received prenalterol. Prenalterol treatment did not influence survival favourably or unfavourably. Five patients had the dose of diuretic increased or a potassium sparing diuretic was added; and nine patients had long acting nitrate drugs added (seven patients) or increased (two patients). Two patients were started on an antiarrhythmic drug, amiodarone. The remaining four patients were referred for cardiac surgery, with subsequent alteration in their drug treatment.

Functional status of survivors

Figure 3 shows the New York Heart Association functional status of survivors. Only seven had a lasting improvement (longer than 12 months) in functional class.

This was attributed to cardiac surgery in two patients and to changes in medical treatment in the remaining five patients (prenalterol three patients, nitrates one patient, and increased diuretics one patient).

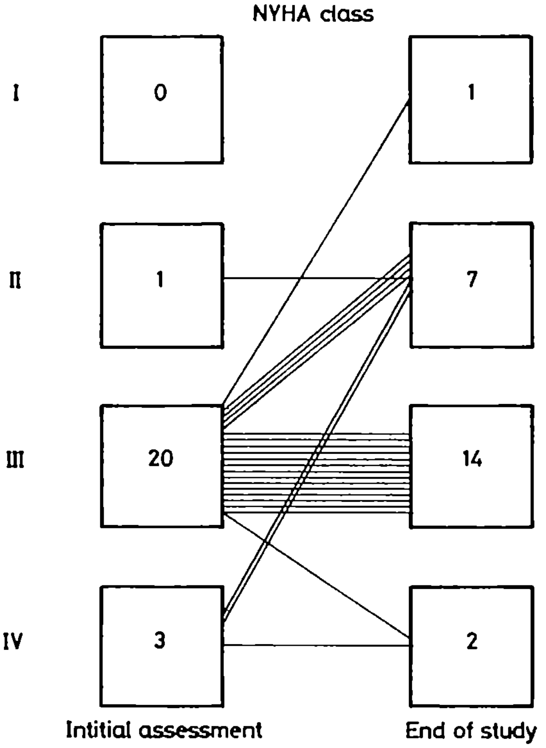

Fig 3 *Functional status of survivors. NYHA, New York Heart Association.*

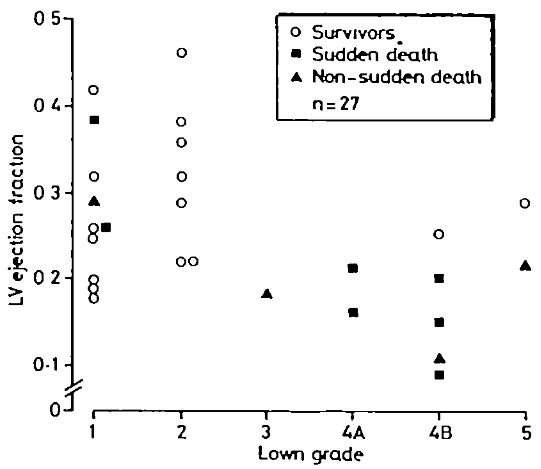

Fig 4 *Left ventricular (LV) ejection fraction versus Lown grade in 27 patients with chronic ischaemic cardiac failure.*

Discussion

The fifty patients who we studied had severe refractory cardiac failure. Their medication at the time of assessment was already comprehensive, with over half of the patients taking drugs with vasodilator activity or "third line" drugs. Nitrates tended to be the most popular, because of their effect in both lowering left ventricular filling pressure and providing prophylaxis against attacks of angina pectoris. The majority of patients had triple vessel coronary artery disease and had had one or more myocardial infarctions and their left ventricular function was very poor. It is therefore not surprising that the mortality was so high and the outcome so poor. Our findings accord with those of many published series.[1-3] We confirmed that those patients with lowest left ventricular ejection fraction are more likely to die.[16] We also confirmed that those patients with the most serious ventricular arrhythmias on an ambulatory electrocardiogram have the worst prognosis.[5 17 18] There appears to be an inverse relation between left ventricular ejection fraction and Lown grade (fig 4); few deaths occurred among patients with a left ventricular ejection fraction >0·30 and the lesser ventricular arrhythmias, whereas mortality was highest in patients with a combination of a very low left ventricular ejection fraction and serious ventricular arrhythmia. Sudden deaths and non-sudden deaths are equally common in this higher risk group. Severe ventricular arrhythmias thus appear to be a marker for severe left ventricular damage.

Current therapeutic practice concentrates on improving the symptoms and status of the left ventricular failure. Our study indicates that some attention should also be paid to these arrhythmias. A similar view has been expressed by Wilson.[13] Conventional antiarrhythmic drugs are, however, often difficult to use in this category of patients because of a deleterious effect on left ventricular function[19] or non-responsiveness to treatment.[20]

The challenge of preventing sudden death in patients with congestive heart failure has recently been reviewed by Packer.[21] Our study was not designed to test the effect of such an intervention.

Treatment was adjusted on an individual basis. We treated only four patients with antiarrhythmic drugs; in every case amiodarone was our choice because it is the least likely of the drugs currently available to depress left ventricular function and its additional antianginal effect may also be beneficial to this class of patient.[22 23] A recent report by Cleland *et al* suggested that amiodarone can successfully suppress ventricular arrhythmias in patients with severe heart failure[24]; however, in this small three month study the impact on survival could not be fully assessed, but it is noteworthy that three patients died suddenly on placebo whereas there were no sudden deaths on amiodarone. Among our four patients, one sudden death occurred in a patient taking amiodarone and the three remaining patients survived.

Sudden death was almost twice as common as death from progressive cardiac failure in our series. This proportion is higher than in the other published series.[3–5] The explanation may lie in the definition of "sudden death" and the selection of patients, although we cannot exclude the possibility that our treatment may have influenced this observation. Short term treatment with prenalterol may cause ventricular arrhythmia when given to susceptible patients,[25] but long term treatment is not associated with increased arrhythmia or mortality; indeed the degree of β blockade perhaps might be useful in preventing arrhythmias.[15] Thirty nine patients were taking digoxin and were in sinus rhythm. Five of the six patients not prescribed digoxin died. There is still controversy about whether long term digoxin treatment provides worthwhile benefits in such patients.[26–28] We did not observe any digoxin toxicity in these patients during follow up and we attribute this to the fact that all these patients were already stabilised on digoxin at the time of assessment. Serum potassium was measured periodically in most patients. No episodes of severe hypokalaemia (serum potassium <3·0 mmol/l) occurred during follow up despite the large doses of frusemide used.

Cardiac surgery, namely resection of a left ventricular aneursym, with or without coronary artery bypass surgery, was only considered suitable for four of the patients. Two further patients had had previous cardiac surgery: one a resection of a left ventricular aneurysm with coronary artery bypass and one a coronary artery bypass alone. The remaining patients were not offered surgery—almost invariably because they had severely reduced left ventricular function without discrete aneurysm. No patient in this series was considered seriously for transplantation; the main reason was that only seven patients were aged <50 years.

Evidence is now accumulating that patients such as ours may have an improved prognosis if coronary revascularisation is performed,[29–31] although the operative and perioperative risks are greater in this group.[31 32] This gradual change in attitudes may mean that a series of patients reported in 10 years time will contain a greater proportion of patients treated surgically.

How then can the outlook be improved for these patients? Undoubtedly optimisation of medical treatment is desirable, and, whenever patients are suitable, cardiac surgery should be carefully considered. Antiarrhythmic drugs should probably be considered although patient selection is difficult. Newer drugs for cardiac failure will continue to attract attention and deserve to be tested in such patients because their prognosis is so poor. Angiotension converting enzyme inhibitors produce clinical benefit[33–35] and there is some evidence to suggest that they reduce arrhythmias[36 37] and may improve the prognosis.[34 35 38] Combined vasodilator treatment with hydralazine and nitrates may also be beneficial.[39] Larger studies are needed to confirm these promising results.

Despite surgery and intensive drug treatment the damage to the left ventricle may be so great that little improvement can be expected whatever therapeutic manoeuvre is attempted. Cardiac transplantation may then be considered for suitable subjects. Predictably the major risk factors for coronary artery disease noted were cigarette smoking (94%) and preceding hypertension (22%).

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References

1 Bruschke AVG, Proudfit WL, Sones FM. Progress study of 590 consecutive non surgical cases of coronary disease followed 5–9 years. II Ventriculographic and other correlations. *Circulation* 1973;47:1154–63.

2 Burggraf GW, Parker JO Prognosis in coronary artery disease Angiographic haemodynamic and clinical factors. *Circulation* 1975;51:146–56.

3 Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;5·831–6.

4 Massie B, Ports T, Chatterjee K, *et al.* Long-term vasodilator therapy for heart failure: clinical response and its relationship to haemodynamic measurements. *Circulation* 1981;63:269–78.

5 Wilson JR, Schwartz JS, St John Sutton M, *et al.* Prognosis in severe heart failure: relation to haemodynamic measurements and ventricular ectopic activity. *J Am Coll Cardiol* 1983;2:403–10.

6 Cohn JN, Levine TB, Olivari MT, *et al.* Plasma norepinephrine as a guide to prognosis in patients with congestive heart failure. *N Engl J Med* 1984; 311:819–23.

7 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441–6.

8 Cohn JN, Franciosa JA. Vasodilator therapy of cardiac failure. *N Engl J Med* 1977;297:27–31.

9 Chatterjee K, Parmley WW. Vasodilator therapy for chronic heart failure. *Annu Rev Pharmacol Toxicol* 1980;20:475–512.

10 LeJemtel TH, Keung E, Sonnenblick EH. Amrinone: a new non-glycosidic non-adrenergic cardiotonic agent effective in the treatment of intractable myo-

cardial failure in man. *Circulation* 1979;**59**: 1098–104.

11 Anonymous. Sympathomimetics in heart failure. *Drug Ther Bull* 1982;**20**:77–8.

12 Anonymous. Beta agonists and heart failure. *Lancet* 1983;**ii**:1063–4.

13 Wilson JR. How and when patients with congestive heart failure die. *Int J Cardiol* 1984;**6**:255–8.

14 Lown B, Wolf M. Approaches to sudden death from coronary heart disease. *Circulation* 1971;**44**:130–42.

15 Glover DR, Wathen CG, Murray RG, Petch MC, Muir AL, Littler WA. Are the clinical benefits of prenalterol in ischaemic heart failure due to beta blockade?: a six month randomised double blind comparison with placebo. *Br Heart J* 1985;**53**: 208–15.

16 Mock MB, Ringquist I, Fisher LD, *et al.* Survival of medically treated patients in the coronary artery surgery study (CASS) registry. *Circulation* 1982;**66**: 562–8.

17 Follansbee WP, Michelson EL, Morganroth J. Non sustained ventricular tachycardia in ambulatory patients: characteristics and association with sudden cardiac death. *Ann Intern Med* 1980;**92**:741–7.

18 Holmes J, Kubo SH, Cody RJ, Kligfield P. Arrhythmias in ischaemic and non-ischaemic dilated cardiomyopathy: prediction of mortality by ambulatory electrocardiography. *Am J Cardiol* 1985;**55**:146–51.

19 Hillis WS, Whiting B. Antiarrhythmic drugs. *Br Med J* 1983;**286**:1332–6.

20 Poll DS, Marchlinski FE, Buxton AE, Doherty JV, Waxman HL, Josephson ME. Sustained ventricular tachycardia in patients with idiopathic dilated cardiomyopathy—electrophysiologic testing and lack of response to antiarrhythmic drug therapy. *Circulation* 1984;**70**:451–6.

21 Packer M. Sudden unexpected death in patients with congestive heart failure: a second frontier. *Circulation* 1985;**72**:681–5.

22 Marcus FI, Fontaine GH, Frank R, Grosgogeat Y. Clinical pharmacology and therapeutic applications of the antiarrhythmic agent, amiodarone. *Am Heart J* 1981;**101**:480–93.

23 Nademanee K, Hendrickson JA, Peterson B, Cannon D, Hecht H, Singh BN. Amiodarone: possibly an ideal antiarrhythmic agent [Abstract]. *Am J Cardiol* 1982;**49**:981.

24 Cleland J, Dargie HJ, Findlay I, Wilson J. Effect of amiodarone on arrhythmia and left ventricular function in heart failure [Abstract]. *Br Heart J* 1985;**54**:647.

25 Capucci A, Fragetti L, Melandri G, Magnani B. Electrophysiological properties of prenalterol. *Int J Cardiol* 1983;**2**:391–400.

26 Selzer A. Digitalis in heart failure. Do benefits justify risks? *Arch Intern Med* 1981;**141**:18–9.

27 Johnston GD, McDeveitt DG. Is maintenance digoxin necessary in patients with sinus rhythm? *Lancet* 1979;**i**:657–70.

28 Petch MC. Digoxin for heart failure in sinus rhythm. *Thorax* 1979;**3**:147–9.

29 Detre K, Peduzzi P, Murphy M, *et al.* Effect of bypass surgery on survival in low and high risk subgroups delineated by the use of simple clinical variables. *Circulation* 1981;**63**:1329–38.

30 Mathur VS, Hall RJ, Garcia E, de Castro CM, Cooley DA. Prolonging life with coronary bypass surgery in patients with three-vessel disease. *Circulation* 1980;**62** (suppl 1):90–7.

31 Isom OW, Spencer FC, Glassman E, Denbrown JM, Pasternack BS. Long term survival following coronary bypass surgery in patients with significant impairement of left ventricular function. *Circulation* 1975;**51** (suppl 1):141–7.

32 Kennedy JW, Kaiser GC, Fisher LD, *et al.* Clinical and angiographic predictors of operative mortality from the collaborative study of coronary artery surgery (CASS). *Circulation* 1981;**63**:793–802.

33 Dzau VJ, Colucci WS, Williams GH, Curfman G, Meggs L, Hollenberg NK. Sustained effectiveness of converting-enzyme inhibition in patients with severe congestive heart failure. *N Engl J Med* 1980;**302**: 1373–9.

34 Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol* 1983; **2**:755–63.

35 Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomised, double-blind study. *Circulation* 1984;**70**:271–7.

36 Cleland JGF, Dargie HJ, Ball SG, *et al.* Effects of enalapril in heart failure: double blind study of effects on exercise performance, renal function, hormones, and metabolic state. *Br Heart J* 1985;**54**:305–12.

37 Cleland JGF, Dargie HJ, Hodsman GP, *et al.* Captopril in heart failure: a double blind controlled trial. *Br Heart J* 1984;**52**:530–5.

38 Furberg C. Yusuf S. Effect of vasodilators on survival in chronic congestive heart failure. *Am J Cardiol* 1985;**55**:1110–3.

39 Cohn JN, Archibald DG, Ziesche S, *et al.* Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986;**314**:1547–52.

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Accurate detection of triple vessel disease in patients with exercise induced ST segment depression after infarction

D MANNERING, E D BENNETT, D E WARD, K DAWKINS, M DANCY,
H VALANTINE, N MEHTA

From the Departments of Medicine One and Cardiology, St George's Hospital and Medical School, London

SUMMARY The severity of coronary artery disease is an important determinant of prognosis after acute myocardial infarction. The ability of a symptom limited exercise test to predict the presence of triple vessel disease was assessed in 221 patients three weeks after infarction. Coronary angiography was performed in patients with exercise induced ST segment depression. The presence of ST segment depression alone was poorly indicative of triple vessel disease; however, some specific features of ST segment changes on exercise were of predictive value. Downsloping ST segment configuration alone or horizontal ST segment depression associated with an early onset and a late recovery time after exercise correctly identified 30 (90%) of 33 patients with triple vessel disease whereas it incorrectly identified only 6 (15%) of 39 patients with single and double vessel disease. An abnormal blood pressure response was also predictive.

In patients with ST segment depression after infarction triple vessel disease can be detected accurately by a combination of the electrocardiographic and haemodynamic variables attained on exercise.

Exercise testing in patients early after myocardial infarction is a valuable diagnostic and prognostic technique. One year mortality in patients with exercise induced ST segment depression has been shown to be 25% compared with 2% in patients with no ST segment depression.[1] Even though the one year mortality rate is significantly higher in patients with ST segment depression on exercise, most of these patients are not at high risk of further cardiac events. There is thus a need to identify more accurately the "at risk" group of patients who may benefit from invasive diagnostic and therapeutic techniques. Furthermore, it has been suggested that reduced exercise tolerance or a poor haemodynamic response on exercise may be more predictive of later complications than ST segment changes.[2]

The purpose of this study was to quantify specific ST segment changes on exercise together with the haemodynamic responses on exercise in a group of patients three weeks after a myocardial infarction and to relate these findings to their subsequent coronary anatomy.

Patients and methods

PATIENTS

The study group consisted of 221 consecutive patients under the age of 70 years in whom the diagnosis of a myocardial infarction was based on the presence of at least two of the following three criteria: (*a*) a typical history of chest pain persisting for at least 30 minutes, (*b*) new Q waves or evolution of ST-T wave changes, (*c*) a rise in the cardiac enzyme concentrations of aspartate transaminase, hydroxybutyrate dehydrogenase, or creatine kinase to at least twice the upper limit of normal. The average (SE) age was 57 (4); 40 (18%) were female. Ninety three (42·2%) had had an anterior infarction, 94 (42 6%) an inferior infarction, 20 (8·9%) a lateral infarction, 4 (2·0%) a true posterior infarction, and 10 (4·4%) had no infarction site indicated by the electrocardiogram. Four showed left bundle branch block and four right bundle branch block on the resting

Requests for reprints to Mr D Mannering, Department of Medicine 1, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE.

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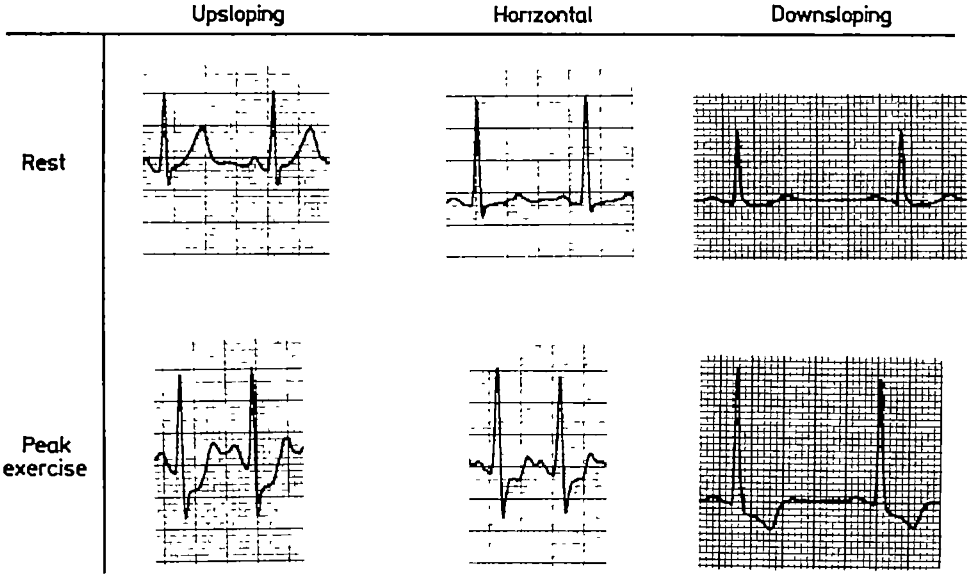

Figure *Characterisation of ST segment configuration at peak exercise.*

electrocardiogram. One hundred and twenty three patients were taking β blockers at the time of exercise. Patients with valvar heart disease or aortic stenosis were excluded from the study.

EXERCISE TESTING

Symptom limited exercise testing was carried out on a motor driven treadmill by the Bruce protocol.[3] Patients exercised for 3 min stages at progressively increasing work loads. A 12 lead electrocardiogram was recorded before exercise with the patient supine and upright, at the end of each 3 minute stage of exercise, immediately after exercise, and every minute during recovery. In addition, leads II, V2, and V5 were continuously monitored throughout exercise. Blood pressure was measured on the right arm by the standard cuff method at the same time as the electrocardiogram was recorded.

Exercise was continued until one of the following end points: (*a*) >3 mm ST segment depression 80 ms after the J point in any lead; (*b*) a fall in systolic blood pressure; (*c*) occurrence of chest pain, dyspnoea, fatigue, or dizziness; (*d*) leg cramps. A test was defined as positive if ⩾1 mm ST segment depression was recorded in any lead. ST segment depression was categorised as slowly unsloping, horizontal, and downsloping configurations (figure). Total exercise time and time to onset of significant ST segment depression on exercise were recorded together with the recovery time from ST segment depression after exercise. The increase in systolic blood pressure at peak exercise was expressed as the percentage increase from the resting value (systolic blood pressure increase). Patients in whom systolic blood pressure did not increase by >10% of the resting value at peak exercise were considered to have a poor exercise blood pressure response. The heart rate at the onset of significant ST depression was expressed as a percentage increase from the resting value (heart rate at onset).

CORONARY ANGIOGRAPHY

Coronary arteriography was performed at 2–4 weeks after the exercise test on patients with significant ST segment depression who agreed to undergo the procedure. Twelve patients with no ST segment depression underwent this procedure for clinical reasons. The arteriograms were viewed by a radiologist who was unaware of the exercise test findings. Significant coronary artery disease was defined as >70% proximal luminal narrowing in either the left anterior descending, circumflex, or right coronary arteries or the left main stem. Patients were then classified as having single, double, or triple vessel disease.

FOLLOW UP

Patients with a diagnosis of significant triple vessel or left main disease were referred for coronary artery bypass surgery together with those patients in whom symptoms persisted despite optimal medical treatment and in whom the coronary anatomy was suitable for surgery. All other patients were managed medically.

STATISTICAL ANALYSIS

Unpaired student *t* tests were applied where appropriate to test for significant differences in the measured exercise variables between the negative and positive test groups and between the patient groups with single, double, and triple vessel disease. We used discriminant analysis (*Statistical Package for the Social Sciences*) to distinguish statistically between patients with (*a*) single and double vessel disease and (*b*) triple vessel disease, using the exercise variables described above as discriminant variables. The optimal discriminatory points were used to determine the sensitivity and specificity of these exercise variables.

Results

Significant ST segment depression (positive test) was recorded in 89 (40%) patients, 72 of whom underwent coronary angiography. The remaining 17 patients with a positive test either refused to undergo this procedure or had more serious underlying medical conditions. Of the patients who underwent angiography, 24 were diagnosed as having single vessel disease, 15 double vessel disease, and 33 triple vessel disease. Of the 132 patients with no ST segment depression (negative test), 12 underwent coronary angiography for clinical reasons: three were <35 years of age, four had significant chest pain, one had a suspected left ventricular aneurysm, one had early exercise induced left bundle branch block, and three became hypotensive on exercise. Single vessel disease was diagnosed in nine, double vessel disease in three; none had triple vessel disease.

There was no significant difference in the resting heart rate between patients with a negative test and those with a positive test (77 beats/minute for both groups) or between the rates attained at peak exercise (127 beats/minute for both groups). Exercise time was significantly longer in patients with a negative test (6·7 (0 3) minutes) than in the positive test group (5 7 (0·3) minutes) ($p < 0{\cdot}01$). The mean (SE) systolic blood pressure increase in the negative test group was 26 (3)% compared with 16 (2)% in the positive test group ($p < 0{\cdot}001$).

Table 1 shows the mean onset time, recovery time, and ST segment configuration together with the systolic blood pressure increase, heart rate increase at ST depression, and the exercise time for the single, double, and triple vessel disease groups together with the respective p values. Table 2 shows the sensitivity and specificity attained for each exercise variable in distinguishing the two groups: (*a*) single and double vessel disease and (*b*) triple vessel disease.

Discriminant analysis demonstrated that downsloping ST segment configuration was the most accurate single exercise variable in predicting severity of disease; it correctly classified 77·8% of patients. This was followed by ST segment recovery time (76·4%); the onset time to significant ST segment depression (75·0%); the increase in heart rate at onset of ST depression (72·2%), and the blood pressure response to exercise (70·8%). By combining all these exercise variables 90·3% of patients were correctly classified ($p < 0{\cdot}01$).

None of the 12 patients with upsloping ST seg-

Table 2 *Sensitivity and specificity of the exercise variables used to distinguish between single and double vessel disease and triple vessel disease*

Exercise variable	*Sensitivity (%)*	*Specificity (%)*
Downsloping ST depression	94 9	57 6
Recovery time from ST depression (≥6 min)	82 1	69 7
Onset time to ST depression (≤3 min)	66 7	84 8
Increase in heart rate at ST depression (<40%)	59 0	87 9
Increase in systolic blood pressure (≤10%)	69 2	72 7
Exercise time (min)	66 7	60 6

able 1 *Mean (SE) values of all exercise variables in relation to the severity of coronary disease*

	Severity of disease			*p values*		
xercise variable	*Single*	*Double*	*Triple*	*Single vs double*	*Single vs triple*	*Double vs triple*
eart rate (rest) (beats/min)	75 (3)	76 (4)	80 (3)	NS	NS	NS
eart rate (peak) (beats/min)	128 (4)	127 (6)	124 (4)	NS	NS	NS
nset time to ST depression (min)	5 5 (0 4)	2 9 (0·4)	2 0 (0·2)	<0 001	<0 001	<0 05
ecovery time from ST depression (min)	3 9 (0 5)	5 3 (0 7)	8 3 (0 5)	NS	<0 001	<0 001
T segment configuration (No)						
Upsloping	11	1	0			
Horizontal	13	12	14		χ^2 p < 0·001	
Downsloping	0	2	19			
stolic blood pressure increase (%)	24·4 (3 2)	15 8 (4 7)	5·1 (2 7)	NS	<0 001	<0 05
crease in heart rate at onset of ST depression (%)	63 4 (5 4)	50 3 (8 8)	29 7 (3 4)	NS	<0 01	<0 001
ercise time (min)	6 9 (0·5)	5 8 (0 6)	4 9 (0·4)	NS	<0·01	NS

Table 3 *Association of early onset time to ST segment depression and late recovery time with severity of disease in patients with horizontal ST segment depression*

Severity of disease	*Group 1* *Onset time >3 min* *Recovery time <6 min*	*Group 2* *Onset time ⩽3 min* *Recovery time <6 min*	*Group 3* *Onset time >3 min* *Recovery time ⩾6 min*	*Group 4* *Onset time ⩽3 min* *Recovery time ⩾6 min*
Single/double vessel	10	8	3	4
Triple vessel	1	1	1	11

ment depression had triple vessel disease whereas 19 of the 21 with downsloping ST segment depression had triple vessel disease. Of the 39 patients with horizontal ST segment depression, however, 14 had triple vessel disease. To separate further this group of patients with horizontal ST segment depression, we used the second and third most powerful discriminant variables (an onset time to significant ST segment depression of ⩽3 minutes and a recovery time after exercise of ⩾6 minutes) in association with horizontal ST segment configuration. Four groups of patients with horizontal ST segment depression were then defined:

Group 1—Patients with an onset time of >3 minutes and a recovery time of <6 minutes.

Group 2—Patients with an onset time of ⩽3 minutes and a recovery time of <6 minutes.

Group 3—Patients with an onset time of >3 minutes and a recovery time of ⩾6 minutes.

Group 4—Patients with onset time of ⩽3 minutes and a recovery time of ⩾6 minutes. Table 3 shows these results.

Seventy nine per cent of the 14 patients with triple vessel disease and horizontal ST segment depression were in group 4 whereas only 16% of those with single or double vessel disease with horizontal ST segment depression were in group 4.

β BLOCKERS

Fifty four (44%) of the 123 patients taking β blockers had significant ST segment depression on exercise compared with 39 (39%) of the 99 patients not taking β blockers. There was no significant difference in the systolic blood pressure increase on exercise between patients taking β blockers (23 (1·7)%) and those who were not (19·8 (2·0)%). There were significant differences in the resting and peak heart rates and the total exercise time between the two groups (table 4).

Table 4 *Mean values (SE) for resting and peak heart rates and exercise time in patients taking β blockers and in those who were not*

	β blockers	*No β blockers*	*p value*
Resting heart rate (beats/min)	68 (2)	90 (2)	<0 001
Peak heart rate (beats/min)	116 (2)	140 (2)	<0 001
Exercise time (min)	6 9 (0 3)	5 8 (0 3)	<0 01

Discussion

We have shown that the presence of exercise induced ST segment depression alone is a poor predictor of severe coronary disease because only 45% of 74 patients with significant ST segment depression had triple vessel disease shown by angiography. This accords with a recent study[4] but not with earlier ones.[5 6] We have demonstrated, however, that further analysis of the ST segment variables can predict more accurately the severity of coronary artery disease.

The absence of downsloping ST segment depression on exercise was the most specific indicator of the absence of triple vessel disease. Of the group with downsloping ST segment depression none had single vessel disease, 9·5% had double vessel disease, and 90 5% had triple vessel disease. Fourteen of the 33 patients with triple vessel disease, however, did not have downsloping ST segment depression. Given the widespread distribution of horizontal ST segment depression in patients with single and double vessel disease and triple vessel disease, further analysis of this configuration would be necessary to determine which ST segment characteristics are of diagnostic value. When exercise induced ST segment depression occurs in patients with triple vessel disease significant ST changes are likely to appear within the first stage of exercise, which was significantly earlier than for single or double vessel disease. Moreover, patients in whom the ischaemic ST segment persists for >6 minutes after exercise are likely to have triple vessel disease. Subdivision of patients with horizontal ST segment depression into those with early onset and late recovery times allows triple vessel disease to be diagnosed with greater accuracy. Eleven (79%) of the 14 patients with triple vessel disease and horizontal ST segment depression had early onset and late recovery times compared with only four (16%) of the 25 with single or double vessel disease with horizontal ST segment depression. When these 14 patients were added to those patients in whom a downsloping configuration was a marker for triple vessel disease 30 (90%) of the 33 patients with triple vessel disease and ST segment depression were correctly identified, with only 6 (15%) of the 39 patients with single and double vessel disease being misclassified.

Specific ST segment analysis can identify triple vessel disease more accurately than the simple presence of ST segment depression, which can only be regarded as a marker for the presence of myocardial ischaemia not its severity.

Recent studies have shown a significant association between a poor systolic blood pressure response on exercise and subsequent cardiac mortality in patients after myocardial infarction.[2 7 8] This abnormal exercise response has been attributed to poor left ventricular function caused by a larger infarct.[9] The results of our study suggest that a poor blood pressure response on exercise is associated with triple vessel disease. This group of patients had a significantly lower blood pressure increase than patients with single or double vessel disease. This observation accords with previous studies.[4 10] Sullivan *et al* reported a significant association between a poor blood pressure response on exercise and multivessel disease.[4] Further, they observed no significant difference in the resting ejection fraction between those patients with a good blood pressure response and those with an inadequate blood pressure response, suggesting that this inadequate response was not a product of poor left ventricular function. These results suggest that a poor blood pressure response may be a function of increased myocardial ischaemia.

No significant differences were seen in the peak heart rate attained on exercise by patients with single, double, and triple vessel disease. In patients with triple vessel disease, however, the increase in heart rate at the onset of significant ST segment depression was lower than in patients with single and double vessel disease. This suggests that patients with severe coronary artery disease increase their heart rate, and thus myocardial oxygen consumption, to a lesser extent before the onset of myocardial ischaemia.

A low maximum heart rate has been shown to be significantly associated with multivessel disease in patients with stable angina.[11] This association is not so clearly demonstrated in patients after myocardial infarction, mainly because there is left ventricular dysfunction. In contrast, Jennings *et al* reported a significant association between a high heart rate at peak exercise and subsequent cardiac mortality and suggested that this was indicative of left ventricular damage rather than the presence of myocardial ischaemia.[2]

The distribution of patients with significant ST segment depression on exercise was not significantly different between patients on β blockers and those who were not. Furthermore, there was no significant difference in the increase in systolic blood pressure on exercise between the two groups. These results suggest that β blockers did not have a significant effect on the ischaemic responses obtained on exercise.

The aim of this study was to attempt to identify within the group of patients with ST segment depression those patients with triple vessel disease. Theroux *et al* reported a one year mortality rate of 25% in patients with exercise induced ST segment depression; only 2% of patients without ST segment depression died.[1] We studied only patients with ST segment depression or a poor haemodynamic response on exercise, and those who had symptoms or were young. Ideally coronary angiography would have been carried out on all patients to determine the distribution of vessel disease in patients with no ST segment depression. We did not consider this approach to be practical or ethical. The prevalence of triple vessel disease in the present study was similar to that previously reported.[12] Additionally, Akhras *et al* in a study of 61 patients undergoing exercise testing and coronary angiography after uncomplicated myocardial infarction found that 43 patients with multivessel disease had ST segment depression compared with only two patients with no ST segment depression.[13] Furthermore, 89% of patients with triple vessel disease were found within the group with exercise induced ST segment depression.[14]

In an attempt to avoid the problems of differentiating between double and triple vessel disease, comparative studies have identified patients as having either single or multivessel disease (double and triple vessel disease).[4 5] Our results have clearly shown that as groups, patients with single, double, and triple vessel disease behave quite differently in terms of their electrocardiographic and haemodynamic responses to exercise. A small proportion of patients with double vessel disease may, however, have exercise responses that resemble those of patients with triple vessel disease. Thus a clear distinction cannot be made between these patients and those with triple vessel disease—an indication of the difficulties of allocating some patients to separate coronary vessel disease groups.

This study has shown that symptom limited exercise testing early after a myocardial infarction is an effective diagnostic technique for identifying patients with severe triple vessel disease. Although we have shown that the presence of ST segment depression alone is a poor indicator of the presence of triple vessel disease, specific analysis of the ST segment changes together with an assessment of the haemodynamic response to exercise can more accurately identify a group of patients who may be at high risk. The simplicity of this approach may be of particular relevance to district hospitals where there are adequate facilities for exercise testing but where access to angiographic techniques is restricted and more accurate identification of patients with suspected triple vessel disease is needed.

References

1 Theroux P, Waters DD, Halphen C, Debaisieux J, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 1979;**301**:341–5

2 Jennings K, Reid DS, Hawkins T, Julian DJ. Role of exercise testing after myocardial infarction in identifying candidates for coronary surgery. *Br Med J* 1984;**288**:185–7.

3 Bruce RA. Exercise testing of patients with coronary heart disease. *Ann Clin Res* 1971;**3**:323–32.

4 Sullivan ID, Davies DW, Sowton E. Submaximal exercise testing early after myocardial infarction: difficulty of predicting coronary anatomy and left ventricular performance. *Br Heart J* 1985;**53**:180–5.

5 Schwartz KM, Turner JD, Sheffield LT, *et al.* Limited exercise testing soon after myocardial infarction; correlation with early coronary and left ventricular angiography. *Ann Intern Med* 1981;**94**:727–34.

6 Fuller CM, Raizer AE, Verani MS, *et al.* Early post myocardial infarction treadmill stress testing; an accurate predictor of multi-vessel coronary disease and subsequent cardiac events. *Ann Intern Med* 1981;**94**:734–9.

7 Handler CE. Submaximal predischarge exercise testing after myocardial infarction; prognostic value and limitations. *Eur Heart J* 1985;**6**:510–7.

8 Fioretti P, Brower RW, Maarten L, *et al.* Prediction of mortality during the first year after acute myocardial infarction from clinical variables and stress test at hospital discharge. *Am J Cardiol* 1985;**55**:1313–8.

9 Grande P, Pedersen A. Myocardial infarct size and cardiac performance at exercise soon after myocardial infarction. *Br Heart J* 1982;**47**:44–50.

10 Starling MR, Crawford MH, Richards KL, O'Rourke RA. Predictive value of early postmyocardial infarction modified treadmill exercise testing in multivessel coronary artery disease detection. *Am Heart J* 1981;**102**:169–75.

11 Thayssen P, Møller M, Haghfelt T, Jagt T. Ventricular arrhythmias in relation to coronary artery stenosis and left ventricular performance. *Eur Heart J* 1982;**3**:35–41.

12 De Feyter PJ, van Eenige MJ, Dighton DH, Visser FC, De Jong J, Roos JP. Prognostic value of exercise testing, coronary angiography and left ventriculography 6–8 weeks after myocardial infarction. *Circulation* 1982;**66**:527–36.

13 Akhras F, Upward J, Scott R, Jackson G. Early exercise testing and coronary angiography after uncomplicated myocardial infarction. *Br Med J* 1982;**284**: 1293–4.

14 Veenbrink Th WG, van der Werf T, Westerhof PW, Robles de Medina EO, Meijler FL. Is there an indication for coronary angiography in patients under 60 years of age with no or minimal angina pectoris after a first myocardial infarction? *Br Heart J* 1985;**53**: 30–5.

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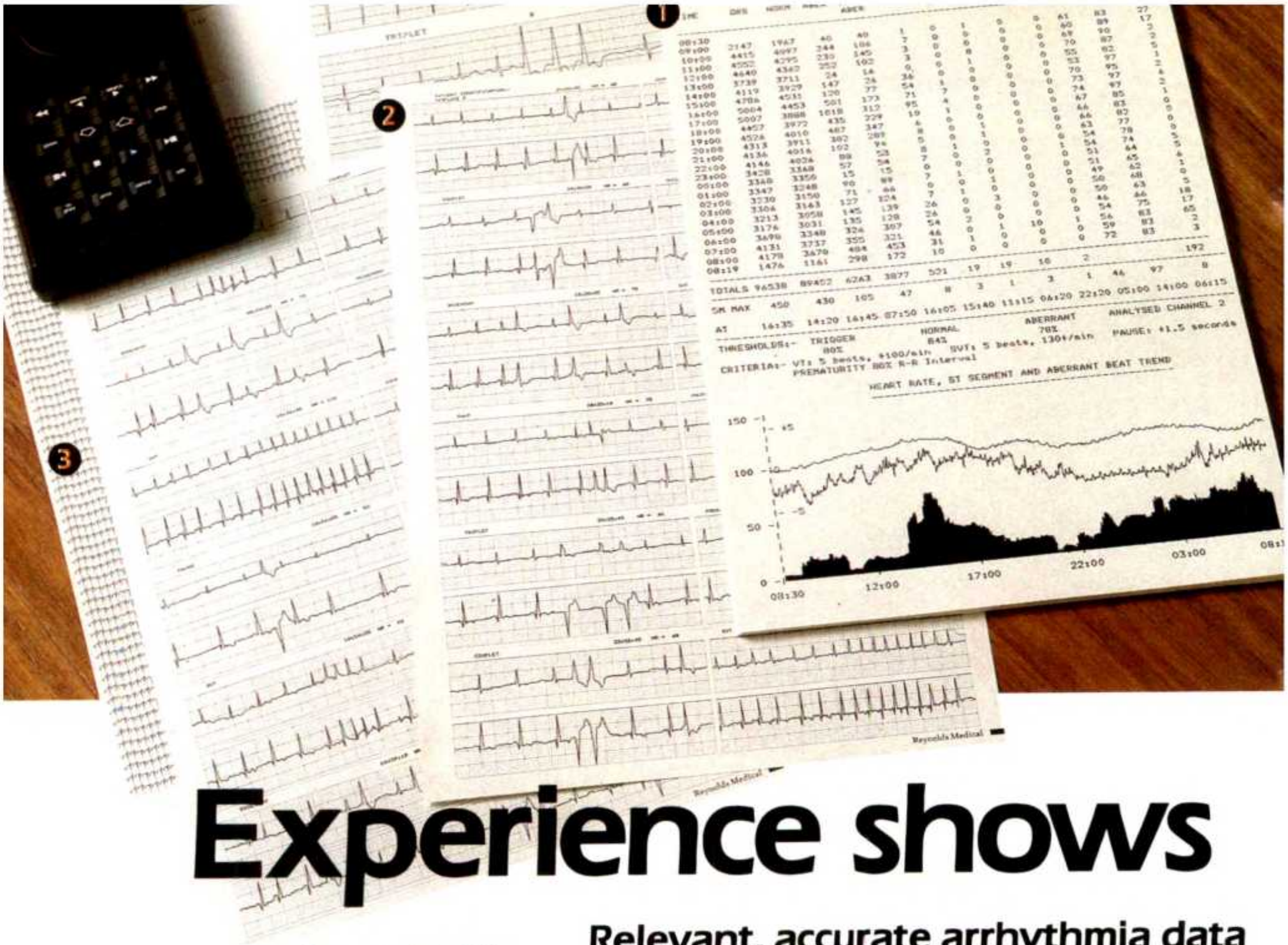

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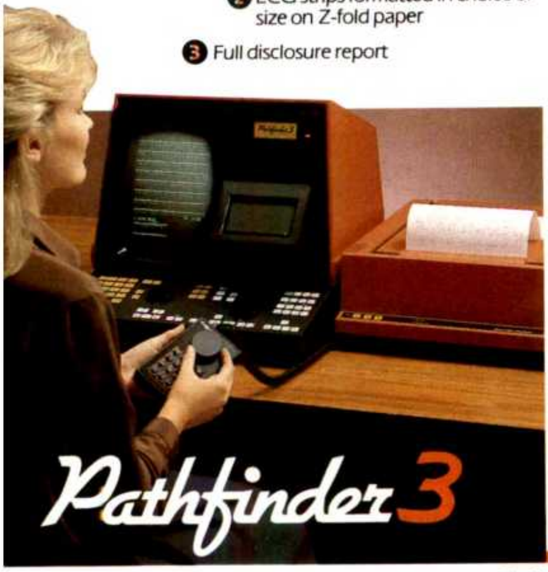

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The right way to automate arrhythmia detection

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Importance of angina for development of collateral circulation

MASATOSHI FUJITA, SHIGETAKE SASAYAMA, AKIRA OHNO, HISAYOSHI NAKAJIMA, HIDETSUGU ASANOI

From the Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Sugitani, Toyama, Japan

SUMMARY The extent of collateral circulation in 46 patients who had intracoronary thrombolysis within six hours of the onset of acute myocardial infarction was evaluated. Patients who had had a previous myocardial infarction (4 cases) or who had spontaneously recanalised infarct related coronary arteries (5 cases) were excluded from the analysis. Collateral development was graded during coronary cineangiography according to the extent of opacification of the collateral and epicardial arteries distal to the site of occlusion (collateral index 0 to 3). Angina was considered to be present before myocardial infarction if it had occurred more than one week before acute myocardial infarction. Collateral channels were visible in only two of 19 patients without angina before infarction and nine of the 18 patients with angina before infarction. The prevalence of angina and the collateral index were not significantly influenced by the extent of coronary vessel disease.

It is concluded that myocardial ischaemia is important in promoting collateral development in man as well as in laboratory animals.

When myocardial ischaemia is caused by severe stenosis of a coronary artery it stimulates the development of collateral vessels between major coronary arteries.[1 2] Some workers have attempted to relate the extent of the development of collateral channels to pre-infarction angina, which is indicative of myocardial inschaemia.[3 4] Collateral perfusion will be less when the diseased arteries are not completely obstructed.[5] In these circumstances, even if there are well developed collateral vessels, collateral flow and corresponding imaging of the collateral channels may be reduced.[6] Thus collateral development in patients with myocardial infarction can only be evaluated accurately when the diseased coronary arteries are occluded. We studied patients who were referred for intracoronary thrombolysis within six hours of the onset of a first myocardial infarction. We selected this group because severe myocardial ischaemia caused by coronary occlusion was likely to have promoted the development of collaterals.[7-9] We studied coronary arteriograms obtained immediately after the onset of the symptoms of acute myocardial infarction to evaluate the effects of myocardial ischaemia on the development of collaterals in these patients.

Patients and methods

Over a five year period 46 patients with acute myocardial infarction were referred for intracoronary thrombolytic treatment within six hours of the onset of symptoms. The diagnosis of acute transmural infarction was established by the presence of acute chest pain lasting >30 minutes and persistent ST segment elevation with or without abnormal Q waves in the standard 12 lead electrocardiogram. We excluded four patients with a history of Q wave infarction and five with subtotal stenosis of an infarct related coronary artery. The remaining 37 patients (31 men and 6 women, mean age 62·5 (range 44–79) had occlusion of one of three major coronary arteries. Pre-infarction angina was defined as typical chest pain occurring more than one week before the acute myocardial infarction. Twenty one patients had an

Requests for reprints to Dr Shigetake Sasayama, The Second Department of Internal Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan.

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anterior infarction and 16 had an infarction at other sites. Coronary artery disease (≥50% reduction in luminal diameter) of one, two, or three vessels was found in 18, 10, and nine patients respectively (table).

CORONARY CINEARTERIOGRAPHY

All patients undergoing selective coronary arteriography in multiple projections by Judkins' or Sones' techniques signed consent forms approved by the university ethics committee. We used a 6 inch Toshiba image intensifier and a 35 mm Ariflex cine camera for arteriography. Two observers who were unaware of the presence or absence of pre-infarction angina in individual patients assessed the cineangiograms and reached a consensus. They classified the degree of opacification of the collateral and epicardial arteries into four grades (collateral index): 0, none; 1, filling of side branches of the artery to be perfused via collateral vessels without visualisation of the epicardial segment; 2, partial filling of the epicardial segment via collateral vessels; 3, complete filling of the epicardial segment via collateral vessels.

STATISTICAL ANALYSIS

We used the χ^2 test to analyse differences between proportions. When necessary we also used Student's *t* test and analysis of variance. A p value of <0·05 was regarded as statistically significant. Results are given as mean (SE).

Results

Eighteen patients (group 1: 60·2 (2·0) years old) had

Table *Data on 37 patients undergoing intracoronary thrombolysis within six hours of the onset of acute myocardial infarction*

Case	*Age (yr)*	*Sex*	*Time (h) until CAG*	*Site of MI*	*Segment* and extent of coronary stenosis (%)*			*CI*
					RCA	*LAD*	*LCX*	
Group 1								
1	52	M	2	Ant	—	6:100	—	0
2	64	M	3	Ant	—	7:100	—	0
3	62	M	5	Ant	—	6:100	—	1
4	45	M	2	Ant	—	6:100	—	1
5	72	M	2	Ant	—	5:100	—	1
6	64	M	5	Ant	—	6:100	—	2
7	44	M	4	Ant	—	7·100	—	2
8	56	M	4	Ant	1:90	7.100	—	0
9	69	F	4	Ant	—	7:100	11.50	0
10	69	M	6	Ant	—	7·100	11:50	0
11	57	M	2	Ant	—	6 100	12:90	0
12	55	M	5	Ant	—	6:100	11·100	2
13	60	M	6	Inf	3·100	—	—	0
14	60	M	6	Inf	4PD:100	—	13 50	1
15	75	M	2	Inf	3:100	6 75	12:75	2
16	62	F	5	Inf	3:100	7:50	11:50	3
17	65	M	2	Post	4PD·75	7:50	11:100	0
18	52	M	5	RV	1.100		—	0
Group 2								
1	46	M	5	Ant	—	6:100	—	0
2	56	M	6	Ant	—	6 100	—	0
3	76	M	4	Ant	—	6:100	—	0
4	71	M	2	Ant	—	6:100	—	0
5	58	F	6	Ant	—	7:100	—	2
6	66	M	4	Ant	1:50	6:100	—	0
7	59	M	6	Ant	4PD 75	6·100	—	0
8	79	F	6	Ant	—	6:100	12:99	0
9	73	M	5	Ant	3:50	7:100	12:50	0
10	47	M	6	Inf	2.100	—	—	0
11	60	M	5	Inf	—	—	13:100	0
12	61	M	2	Inf	3·100	—	—	0
13	68	M	3	Inf and Post	—	—	13·100	0
14	53	M	4	Inf	—	7:75	15:100	0
15	72	F	5	Inf	1:50	6:75	13:100	0
16	57	M	4	Inf	1:100	8:90	11 75	0
17	78	M	3	Inf	1:100	7:50	13.90	0
18	73	F	6	Inf and RV	1 100	7:100	12:90	0
19	74	M	4	Inf	2 100	9:75	13:75	1

Ant, anterior infarction; CAG, coronary arteriography, CI, collateral index, Inf, inferior infarction, LAD, left anterior descending coronary artery, LCX, left circumflex coronary artery, MI, myocardial infarction; PD, posterior descending coronary artery; Post, posterior infarction; RCA, right coronary artery; RV, right ventricular infarction.

*Coronary artery segments were identified and categorised according to a reporting system proposed by the American Heart Association.[14]

Group 1 had pre-infarction angina and group 2 did not.

pre-infarction angina and the remaining 19 patients (group 2, aged 64·6 (2·3)) had not reported angina before infarction (table). Coronary arteriography was carried out 3·9 (0·4) hours after the onset of acute myocardial infarction in group 1 and 4 5 (0·3) hours in group 2 (table).

The prevalence of pre-infarction angina was not influenced by the site of infarction. Pre-infarction angina was reported in 12 (57%) of 21 patients with anterior infarction and six (38%) of 16 with infarction at other sites. The proportion of patients with angina was similar whatever the extent of coronary vessel disease (9/18 (50%) in one vessel disease; 6/10 (60%) in two vessel disease; 3/9 (33%) in three vessel disease).

The presence of pre-infarction angina was the fac-

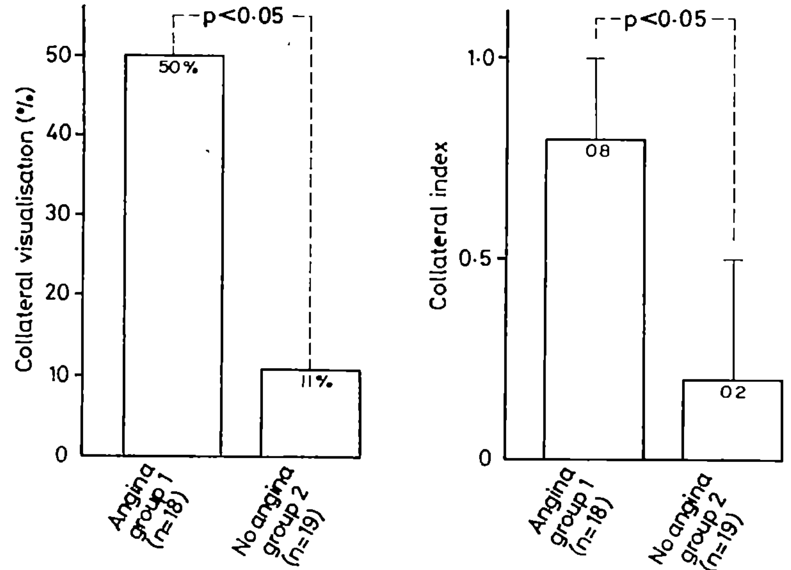

Fig 1 *Collateral visualisation and collateral index in patients with or without pre-infarction angina pectoris.*

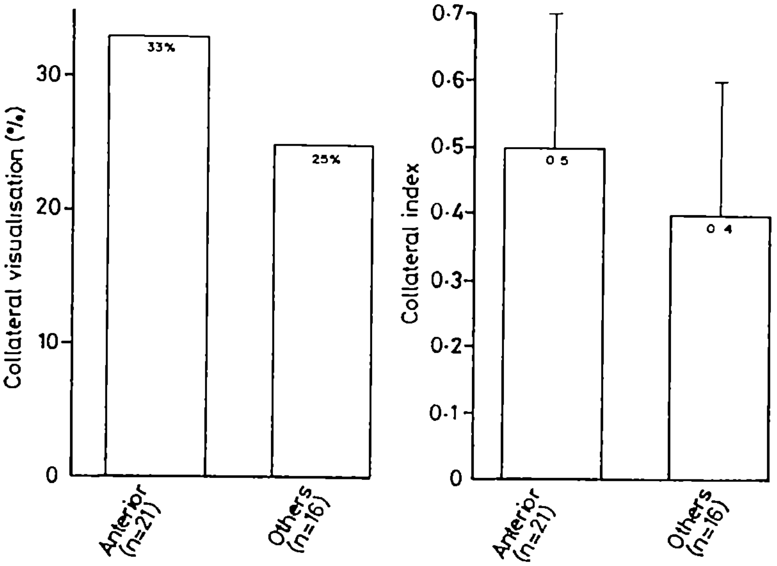

Fig 2 *Collateral visualisation and collateral index in patients with anterior infarction and in those with infarction at other sites.*

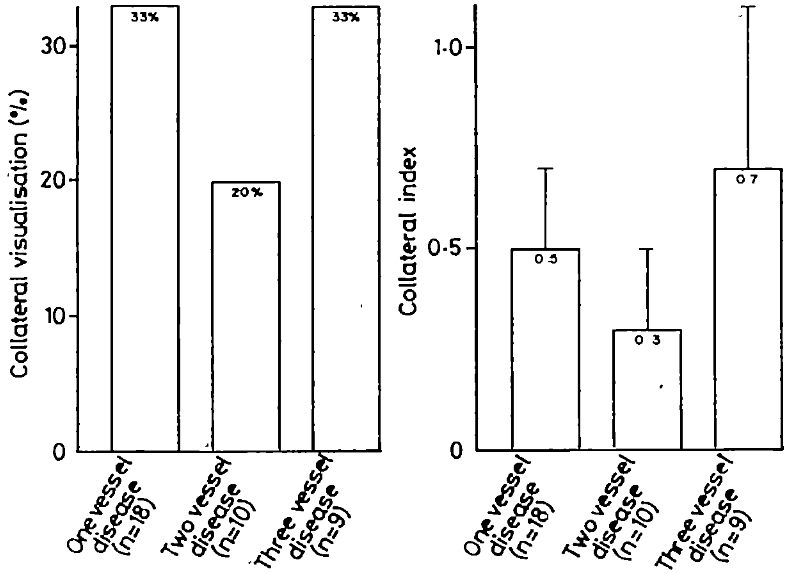

Fig 3 *Collateral visualisation and collateral index in patients with the various degrees of severity of coronary vessel disease.*

tor that was most strongly associated with the development of collateral vessels. Collateral channels were visualised in nine (50%) of 18 patients with pre-infarction angina (group 1) and in only two (11%) of 19 patients without (group 2) ($p < 0{\cdot}05$). The collateral index was significantly higher in group 1 (0·8 (0·2)) than in group 2 (0·2 (0·3)) (fig 1).

The site of infarction did not significantly affect the proportion of patients showing collateral opacification. This was seen in seven (33%) of the 21 patients with anterior infarction and in four (25%) of the 16 with infarction of other sites. The collateral index was also similar in both groups (0·5 (0·2) *vs* 0·4 (0·2)) (fig 2).

The proportion of patients in whom collateral flow was visualised was similar in groups with one vessel disease (6/18, 33%), two vessel disease (2/10, 20%), and three vessel disease (3/9, 33%). These groups also had similar collateral indexes (0·5 (0 2), 0·3 (0·2), and 0·7 (0 4) respectively) (fig 3).

Discussion

Some patients with occlusion of one or more of major coronary arteries do not experience myocardial ischaemia at rest because an adequate blood supply is maintained through well developed collateral channels.[10] Other groups have emphasised the importance of collaterals in preserving left ventricular function after acute myocardial infarction.[3 11 12] Little is known, however, about collateral development at the onset of myocardial infarction.

There are conflicting reports on the relation between preceding angina and of the prevalence of collateral development after acute myocardial infarction.[3 4] Aygen reported that 70 out of 81 patients with the history of pre-infarction angina had adequate collaterals, whereas only five of 19 patients without pre-infarction angina showed collaterals.[4] Aygen may have seen more collaterals in his patients than we saw in our group because the interval between the onset of acute infarction and coronary angiography was longer than in our study.[9]

We examined our patients by coronary arteriography within six hours of the development of severe anterior chest pain. Schaper *et al* demonstrated that it takes at least eight hours for cells in the collateral vessels to start proliferating after the abrupt occlusion of canine coronary arteries.[13] Therefore, it seems unlikely that collateral channels will develop if severe myocardial ischaemia is short lived. Thus it seems reasonable to suggest a relation between pre-existing myocardial ischaemia and the extent of collateral circulation during the acute phase of myocardial infarction.

Williams *et al* also reported that five of nine patients with pre-infarction angina had adequate collaterals whereas only one of 11 patients without angina before infarction had angiographic evidence of adequate collaterals.[3] Although the frequency with which collaterals were visualised in their study resembled our findings, their results must be interpreted with caution because the interval of 15 days from the onset of acute infarction to cardiac catheterisation may well have permitted collateral development. On the other hand, 11 of their 20 patients had subtotal obstruction of the infarct related coronary artery. When the collateral circulation is assessed in the absence of total obstruction of the diseased coronary artery, collateral function may be underestimated. Indeed, Rentrop *et al* showed that the visualisation rate of collateral vessels was substantially increased by the complete occlusion of the coronary artery by an angioplasty balloon.[6] These two factors will have had opposing effects on collateral visualisation in the study of Williams *et al.*[3]

In our study half of the patients with pre-infarction angina had well developed collaterals. In those who did not, stenosis of an artery supplying the collateral vessel could have reduced the pressure gradient across the collateral network and hence collateral perfusion. This was not the case in these patients, however, because there were no differences in the severity of coronary atherosclerosis between patients with and without collaterals. Moreover, the frequency of angiographically displayed collaterals was similar for anterior infarcts and infarcts of other sites. Consequently, these variations in developing collaterals appear to be related to disparities in individual responsiveness to ischaemic stimulation or differences in total amount of myocardial ischaemia.

Seventeen of 19 patients without pre-infarction angina had no angiographically visualised collaterals. The prognosis of patients without collaterals at the time of acute myocardial infarction is worse than that in those with well developed collaterals.[3 11 12] Accordingly, the prevention of the factors initiating myocardial infarction must be of particular importance in managing patients with minimum ischaemic symptoms.

References

1 Litvak J, Siderides LE, Vineberg AM. The experimental production of coronary artery insufficiency and occlusion. *Am Heart J* 1957;53:505–18.

2 Elliot EC, Jones EL, Bloor CM, Leon AS, Gregg DE. Day-to-day changes in coronary hemodynamics secondary to constriction of circumflex branch of left coronary artery in conscious dogs. *Circ Res* 1968;22:237–50.

3 Williams DO, Amsterdam EA, Miller RR, Mason DT. Functional significance of coronary collateral vessels in patients with acute myocardial infarction: relation to pump performance, cardiogenic shock and survival. *Am J Cardiol* 1976;37:345–51.

4 Aygen M. Collateral circulation and regional myocardial function. *Bibl Cardiol* 1977;36:136–40.

5 Gregg DE. *Coronary circulation in health and disease.* Philadelphia: Lea and Febiger, 1950:187–202.

6 Rentrop KP, Cohen M, Blanke H, Phillips RA. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587–92.

7 Pasyk S, Bloor CM, Khouri EM, Gregg DE. Systemic and coronary effects of coronary artery occlusion in the unanesthetized dog. *Am J Physiol* 1971;220: 646–54.

8 Bloor CM, White FC. Functional development of the coronary collateral circulation during coronary artery occlusion in the conscious dog. *Am J Pathol* 1972;67:483–500.

9 Ohgitani N. Time-delay of visualisation of coronary collaterals after the onset of myocardial infarction. *Jpn Circ J* 1977;41:1277–8.

10 Freedman SB, Dunn RF, Bernstein L, Morris J, Kelly DT. Influence of coronary collateral blood flow on the development of exertional ischemia and Q wave infarction in patients with severe single-vessel disease. *Circulation* 1985;71:681–6.

11 Rogers WJ, Hood WP, Mantle JA, *et al.* Return of left ventricular function after reperfusion in patients with myocardial infarction: importance of subtotal stenoses or intact collaterals. *Circulation* 1984;69:338–49.

12 Saito Y, Yasuno M, Ishida M, *et al.* Importance of coronary collaterals for restoration of left ventricular function after intracoronary thrombolysis *Am J Cardiol* 1985;55:1259–63.

13 Schaper W, De Bravander M, Lewi P. DNA synthesis and mitoses in coronary collateral vessels of the dog. *Circ Res* 1971;28:671–9.

14 Austen WG, Edwards JE, Frye RL, *et al.* A reporting system on patients evaluated for coronary artery disease. *Circulation* 1975;51 (suppl IV):IV-5–40.

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What proportion of patients with myocardial infarction are suitable for thrombolysis?

NEIL MURRAY, JOHN LYONS, CLIVE LAYTON, RAPHAEL BALCON

From the Department of Cardiology, London Chest Hospital, London

SUMMARY Four hundred and three patients were considered for entry into a trial of intravenous streptokinase in suspected myocardial infarction. Three hundred and sixty seven (91%) were excluded. Two hundred and sixty (65%) did not meet the inclusion criteria and 45 of the remaining 143 (35%) patients had contraindications to thrombolysis. This left 98 (24%) patients who were suitable for thrombolysis and 42 of them were over 70 years, the upper age limit. Thus according to this trial protocol 56 (14%) patients were eligible for recruitment; 36 (9%) patients were finally randomised. These data suggest that treatment with intravenous streptokinase may be applicable to only a small proportion of patients with myocardial infarction.

Experimental work has shown that early reperfusion after coronary artery occlusion limits myocardial damage.[1] For this reason there is much current interest in the use of thrombolysis in the management of acute myocardial infarction. Reperfusion of the infarct related coronary artery by a direct intracoronary infusion of agents such as streptokinase occurs in approximately 75% of patients.[2-4] Some studies have shown improvement in left ventricular function[5] and short term survival.[6] The application of intracoronary thrombolysis is, however, limited because it requires facilities for emergency coronary angiography, which are not widely available, particularly outside normal working hours.

Intravenous administration of a thrombolytic agent is a more practical approach. Early studies of 24 hour infusion regimens produced inconsistent results[7 8] and this treatment was not generally accepted. More recent trials have shown that high dose infusions of shorter duration produce a rate of clot lysis of approximately 60%[3]—a rate that is only slightly lower than that obtained with intracoronary administration. Indeed, some workers believe that ultimately clot lysis may occur as frequently with intravenous as with intracoronary administration.[3 9] Good responses in left ventricular function[10] and short term survival[11] have been achieved by both methods. Intravenous administration has, therefore, been put forward as a technique that could be generally applied in clinical practice.

Certain problems may limit the use of thrombolytic treatment. Firstly, patients must be selected with care if haemorrhage and hypersensitivity are to be avoided. Secondly, thrombolysis should probably be performed within six hours of the onset of symptoms[1] if myocardial salvage is to be achieved. Even in well equipped centres treatment will be delayed to allow for the coronary angiography that is required before intracoronary thrombolysis can be performed. The inverse relation between the amount of myocardial salvage and the time between coronary occlusion and clot lysis makes the intravenous route more attractive. Prehospital delays may, however, be as important as in hospital ones, and they apply equally to intravenous and intracoronary administration. Thus it may be that although intravenous thrombolysis has been widely advocated, it may not be as applicable as was at first thought.

We are currently engaged in a multicentre trial to investigate the role of high dose intravenous streptokinase in suspected myocardial infarction. We report the reasons for the exclusion of patients from the trial. This should indicate the proportion of patients with suspected myocardial infarction who will be suitable for thrombolysis.

Requests for reprints to Dr Neil Murray, The Regional Cardiac Centre, Groby Road Hospital, Leicester LE3 9QE

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Patients and methods

All patients presenting with a clinical diagnosis of suspected myocardial infarction were considered for entry into the trial. The inclusion criteria were (*a*) chest pain suggestive of myocardial infarction, (*b*) admission to hospital at such a time that treatment could begin within six hours from the onset of symptoms, and (*c*) the presence on the electrocardiogram of 1 mm ST segment elevation in the standard leads or 2 mm in the precordial leads on admission and at least 30 minutes after the onset of symptoms.

Exclusion criteria were: (*a*) cerebrovascular disease; (*b*) history of peptic ulceration or other disease with bleeding tendency; (*c*) blood pressure > 180/110 mm Hg on admission; (*d*) surgical treatment within the previous four weeks; (*e*) cardiopulmonary resuscitation or central vascular cannulation before treatment started; (*f*) previous entry into the trial or previous treatment with streptokinase; (*g*) valvar heart disease with atrial fibrillation; (*h*) diabetes for which insulin treatment had been started before the patient was 30; (*i*) anticoagulant treatment; (*j*) current pregnancy; (*k*) age > 70 years. These exclusion criteria were chosen to avoid the predictable complications of streptokinase and they are standard for a trial of this nature. The reasons for the exclusion of patients were examined. Patients could have had more than one reason for exclusion. Thus the inclusion criteria were considered first, in the order stated, and we considered the exclusion criteria only in those patients in whom all the inclusion criteria were fulfilled. Exclusion criteria were also considered in the order stated. Once we knew of one reason for a patient to be excluded we did not seek further reasons.

Results

During the period October 1984 until June 1985 403 patients (277 men and 126 women) presented to the participating centres with a clinical diagnosis of suspected acute myocardial infarction and were considered for entry into the trial (figure). The mean age of the patients was 66·2 years (men 63·7 and women 71·2, range 24–92).

Two hundred and sixty (65%) patients did not meet the inclusion criteria: 19 (5%) reported atypical symptoms despite a clinical diagnosis of suspected myocardial infarction, 157 (39%) presented more than six hours after the onset of symptoms, and 84 (21%) did not demonstrate the required electrocardiographic changes.

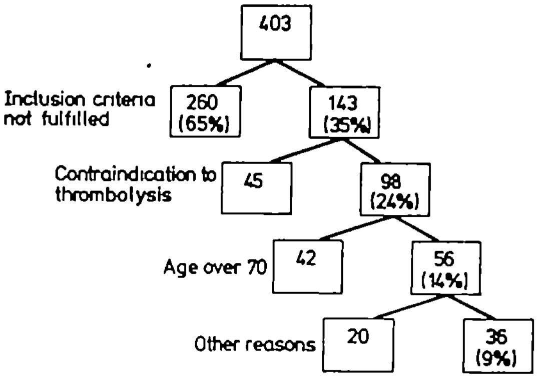

Figure *Reasons for exclusion of patients from a trial of intravenous streptokinase in myocardial infarction*

Forty five of the 143 patients who did fulfil the inclusion criteria had specific contraindications to thrombolysis as defined by the trial protocol (table 1). The most important reasons for exclusion were history of peptic ulceration, systemic hypertension, and resuscitation.

Thus 98 (24%) patients were suitable for thrombolysis. Of these, 42 were over the age of 70 years and were excluded on this criterion alone. Therefore, 56 (14%) patients were eligible for recruitment. Finally 36 (9%) were recruited. The reasons for the exclusion of the remaining 20 were inability to obtain consent in six patients, cardiac arrest before randomisation in two, and local administrative reasons in twelve.

Discussion

These data suggest that only a small proportion of patients with acute myocardial infarction are suitable for thrombolysis if the criteria used in this study are applied. This has two implications. First, any conclusions about efficacy of thrombolysis can only be applied to this group of patients. Secondly, if thrombolysis becomes clinically useful it may be inappropriate for over three quarters of all patients with myocardial infarction. This does not reduce the

Table 1 *Patients excluded because of contraindications to thrombolysis*

Contraindication	*No patients*
Cerebrovascular disease	5
Peptic ulcer/bleeding	10
Blood pressure > 180/110 mm Hg	13
Recent operation	1
Resuscitation	12
Previous streptokinase	0
Valve disease	0
Diabetes	2
Anticoagulants	2
Pregnancy	0
Total	45

value of thrombolysis in patients who are suitable and in whom it may prove to be very useful.

The problem of patient recruitment is common to many thrombolysis trials. Khaja *et al* recruited 54 (18%) of a possible 305 patients into a trial of intracoronary streptokinase.[12] There was no upper age limit in this protocol, although patients had to present within six hours of the onset of symptoms. The European cooperative trial of intravenous streptokinase, published in 1979, set a time limit of 12 hours from symptom onset and required a birthdate of 1900 or later for inclusion.[8] These workers stratified 512 (22%) of 2338 patients and finally randomised 315 (13·5%). In the treatment group there were 31 patients (12 streptokinase, 19 placebo) in whom the 12 hour limit was exceeded. A recent study by Sainsous *et al* reported that of 1105 patients with myocardial infarction 175 (15·8%) were suitable for intravenous thrombolysis.[13]

Low recruitment rates are a feature of other infarct intervention studies. Lie *et al* recruited 29% of all patients with infarcts into a trial of lignocaine,[14] Yusuf *et al* randomised 10–20% of all possible patients into a trial of atenolol,[15] and Muller *et al* recruited 8% into a study of nifedipine.[16] Contraindications to treatment varied in the trial protocols but important factors for the low recruitment rates in all these trials were the age of the patients and the time taken for them to present.

Attempts to widen the application of thrombolysis could be aimed at the reasons for exclusion of patients as described above. If the treatment is to remain safe, however, the number of patients with contraindications to specific treatments with different thrombolytics is unlikely to be reduced. Recruitment would be improved if a thrombolytic agent with fewer side effects could be developed. There is a great deal of interest in new agents, particularly tissue plasminogen activator. Tissue plasminogen activator is claimed to have very little systemic effect. Early results, however, show an incidence of haemorrhage similar to that with high dose streptokinase.[17] It would be difficult, therefore, to use tissue plasminogen activator in patients with almost any one of our exclusion criteria. Hypersensitivity will not be a problem because tissue plasminogen activator is not antigenic; but nor is streptokinase if patients are premedicated with hydrocortisone.

Reducing the time taken for patients to present would be important. Sainsous *et al* reported a mean in hospital delay of 10·3 (10·5) hours; patients presenting more than 48 hours after infarction were excluded.[13] This delay could be reduced by patient education and the use of mobile coronary ambulances.[18] Public education in cardiopulmonary resuscitation may also increase the number of so called "sudden death survivors" who may prove suitable for thrombolysis.[19]

Table 2 *Patients excluded on the grounds of age alone (cumulative frequency)*

Upper age (yr)	*Additional number of patients suitable*
71	1
72	3
73	8
74	11
75	18
76	22
77	25
78	27
79	29
80	34
90	40
100	42

The question of age is complex. The upper age limit for this study was 70 years. Forty two patients were excluded on the basis of age alone. If the upper age limit were to be raised to 75 years a further 18 patients would be recruited (table 2). By raising it to 80 years a total of 34 extra patients would be eligible for the trial, thus increasing the proportion of suitable patients to 22%. This may be a useful way of improving recruitment if it is shown that long term survival is improved by thrombolysis alone and that the incidence of complications is no higher in this older age group. If future studies indicate that survival after thrombolysis can only be improved by subsequent coronary angioplasty or bypass grafting it might be inappropriate to consider this treatment in patients over the age of 70 because surgical intervention is usually considered in these patients only when angina is severe. A recent study from Verheugt *et al* has indicated that haemorrhage is more frequent after intracoronary thrombolysis in patients over the age of 60.[20] If this trend applies over the age of 70 then this consequence would also have to be considered.

We believe, therefore, that although thrombolysis, with or without subsequent angioplasty or surgery, may lead to improved long term survival, this treatment may be applicable to only a small proportion of patients with myocardial infarction.

References

1 Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischaemic cell death 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 1977;56:786–98.

2 Rentrop KP, Feit F, Blanke H, *et al*. Effects of intracoronary streptokinase and intracoronary nitroglycerin infusion on coronary angiographic patterns and mortality in patients with acute myocardial infarction. *N Engl J Med* 1984;311:1457–63.

3 Alderman EL, Jutzy KR, Berte LE, *et al.* Randomized comparison of intravenous versus intracoronary streptokinase for myocardial infarction. *Am J Cardiol* 1984;**54**:14–9.

4 Kennedy JW, Gensini GG, Timmis GC, *et al.* Acute myocardial infarction treated with intracoronary streptokinase: a report of the Society for Cardiac Angiography. *Am J Cardiol* 1985;**55**:871–7.

5 Anderson JL, Marshall HW, Bray BE, *et al.* A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction. *N Engl J Med* 1983;**308**:1312–8.

6 Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington Randomized Trial of Intracoronary Streptokinase in Acute Myocardial Infarction. *N Engl J Med* 1983;**309**:1477–82.

7 Aber CP, Bass NM, Berry CL, *et al.* Streptokinase in acute myocardial infarction: a controlled multicentre study in the United Kingdom. *Br Med J* 1976; **ii**:1100–4.

8 European Study Group for Streptokinase in Acute Myocardial Infarction. Streptokinase in acute myocardial infarction. *N Engl J Med* 1979;**301**:797–802.

9 Schroder R. Systemic versus intracoronary streptokinase infusion in the treatment of acute myocardial infarction. *J Am Coll Cardiol* 1983; **1(5)**:1254–61.

10 Anderson JL, Marshall HW, Askins JC, *et al.* A randomized trial of intravenous and intracoronary streptokinase in patients with acute myocardial infarction. *Circulation* 1984;**70**:606–18.

11 Simoons ML, Serruys PW, Brand M, *et al.* Improved survival after early thrombolysis in acute myocardial infarction. *Lancet* 1985;**ii**:578–82.

12 Khaja F, Walton JA, Brymer JF, *et al.* Intracoronary fibrinolytic therapy in acute myocardial infarction: report of a prospective randomized trial. *N Engl J Med* 1983;**308**:1305–11.

13 Sainsous J, Serradimigni A, Richard JL, Guize L, LeConte T, Tanielian PH. How many patients with acute myocardial infarction could be treated in France by intravenous streptokinase? Results of a prospective trial [Abstract]. *Eur Heart J* 1985;**6**(suppl I):67.

14 Lie KI, Wellens HJ, van Capelle FJ, Durrer D. Lidocaine in the prevention of primary ventricular fibrillation. A double-blind, randomized study of 212 consecutive patients. *N Engl J Med* 1974;**291**:1324–6.

15 Yusuf S, Sleight P, Rossi P, *et al.* Reduction in infarct size, arrhythmias and chest pain by early intravenous beta blockade in suspected acute myocardial infarction. *Circulation* 1983;**67**(suppl I):I.32–41.

16 Muller JE, Morrison J, Stone PH, *et al.* Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison. *Circulation* 1984; **69**:740–7.

17 The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) trial. Phase I findings. *N Engl J Med* 1985;**312**:932–6.

18 Mathewson ZM, McCloskey BG, Evans AE, Russell CJ, Wilson C. Mobile coronary care and community mortality from myocardial infarction. *Lancet* 1985; **i**:441–3.

19 Cobb LA, Baum RS, Alvarez H, Schaffer WA. Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow-up. *Circulation* 1975;**52**(suppl III): 223–35.

20 Verheugt FWA, van Eenige MJ, Res JCJ, *et al.* Bleeding complications of intracoronary fibrinolytic therapy in acute myocardial infarction: assessment of risk in a randomized trial. *Br Heart J* 1985;**54**:455–9.

Br Heart J 1987;57:148–53

Diurnal variation in left ventricular function: a study of patients with myocardial ischaemia, syndrome X, and of normal controls

RICHARD D LEVY, DAVID CUNNINGHAM, LEONARD M SHAPIRO,
CHRISTINE WRIGHT, LORNA MOCKUS, KIM M FOX

From the National Heart Hospital, London

SUMMARY Angina can occur in the early morning. The mechanism of this is unclear and both haemodynamic changes and coronary artery spasm may be important. The purpose of this study was to investigate the diurnal variation in pulmonary artery diastolic pressure (an indirect measure of left ventricular filling pressure) in six normal subjects, 18 patients with coronary artery disease, five with variant angina, and six with syndrome X. A transducer tipped catheter and a simple recording system were used to record ambulatory pulmonary artery diastolic pressure for 24 hours. Variation in pulmonary artery diastolic pressure was related to the timing of episodes of ST segment depression and elevation by simultaneously recording a frequency modulated electrocardiogram. Episodes of ST segment change occurred predominantly in the early morning (midnight to 6 am) in variant angina (eight out of 14 episodes) whereas in syndrome X all episodes were recorded during the day. In coronary artery disease both painful and painless episodes were distributed throughout the day, with 10 out of 67 episodes occurring between midnight and 6 am. A similar diurnal variation in pulmonary artery diastolic pressure was seen in the groups—that is, values were low during the day and higher at night, with the maximum values between midnight and 6 am. The 24 hour median pulmonary artery diastolic pressure was higher in patients with coronary artery disease than in the control group and those with syndrome X.

The finding that pulmonary artery diastolic pressure, and therefore left ventricular end diastolic pressure, is greatest in the early morning may represent the background haemodynamic state in which other factors lead to myocardial ischaemia during these hours.

There is a well described diurnal variation in several physiological variables such as blood pressure, heart rate, cortisol, and catecholamines.[1–4] This may have adverse consequences; for example myocardial infarction and cerebral infarction both show diurnal variation.[5 6] Angina may occur not only when the patient is active through the day but also in the early hours of the morning.[7–9] Various pathophysiological mechanisms have been proposed, including an increase in myocardial oxygen consumption in patients with severe coronary artery disease and coronary spasm in patients with variant angina.[10 11] Angina decubitus, first described by Heberden, is probably caused by increased left ventricular filling pressure secondary to increased venous return when the patient lies down in bed.[12] It has not been possible previously to investigate the importance of left ventricular filling pressure as a mechanism of myocardial ischaemia.

We have developed a technique for recording ambulatory pulmonary artery diastolic pressure.[13] This provides a means of assessing left ventricular filling pressure in normal subjects and patients with ischaemic heart disease during unrestricted activity. The purpose of this study was to determine whether there is diurnal variation in left ventricular filling pressure, because this may have an important bearing on the pathophysiological mechanisms of nocturnal angina.

Requests for reprints to Dr Richard D Levy, Department of Cardiology, St Bartholomew's Hospital, West Smithfield, London EC1 7BE.

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Patients and methods

We studied 29 patients (28 men, 1 woman). All were shown on the basis of clinical history and coronary angiography to have various coronary ischaemic syndromes. Eighteen patients had atherosclerotic coronary artery disease (mean (SD) age 57 (11) years), five patients had variant angina (mean age 51 (8) years) and six patients had syndrome X (mean age 48 (12) years).

Normal controls—Six control subjects (5 men, 1 woman) were studied (mean age 39 (6·6) years). These subjects presented with atypical chest pain; they had negative exercise tests and normal coronary arteries at angiography. The results of 24 hour ambulatory ST segment monitoring was entirely normal.

Coronary artery disease—All had angiographic evidence of coronary artery disease: 14 had three vessel disease, three had two vessel disease, and one had single vessel disease.

Variant angina—These patients had clinical, and angiographic or electrocardiographic evidence or both of coronary artery spasm: one had normal coronary arteries and four had coronary artery disease.

Syndrome X—These were patients who gave a history of chest pain but were shown to have normal coronary arteries despite a positive exercise test with at least 1 mm ST segment depression recorded on exercise.

All antianginal medication other than glyceryl trinitrate was discontinued at least 48 hours before the study. The pulmonary artery pressure was monitored for at least 24 hours and where possible for up to 48 hours. The frequency modulated ST segment was monitored throughout this period.

The study was approved by the ethics committee and the patients gave their informed consent.

The transducer tipped pulmonary artery catheter was introduced percutaneously via the subclavian vein to a proximal pulmonary artery under fluoroscopic control in the cardiac catheter laboratory when the patient had cardiac catheterisation. A polyurethane six French NIH type catheter with a miniature strain gauge transducer mounted on the tip was used. The transducer was driven and demodulated by an electrically isolated Gaeltec amplifier. Pulmonary artery pressure was recorded on an Oxford Medilog 1 miniature tape recorder that had been modified by the insertion of an AM4 pressure module.

The ST segment was monitored on a frequency modulated recorder and leads CM2 and CM5 were recorded. The electrocardiogram was replayed on an Oxford MA20 scanner. Changes in the ST segment were measured 80 ms after the J point. A change of 1 mm ST segment depression was considered significant. The heart rate and ST segment changes were analysed on a beat to beat basis for five minutes before each episode and again for five minutes after the ST segment had returned to basal levels.

Patients were then asked to perform normal daily activities and were fully ambulant during the 24 hours of recording. Patients kept diaries during the period that ambulatory pulmonary artery pressure and the ST segment were monitored. The pulmonary artery pressure trace was replayed via a PB2 unit and a PM3 amplifier. Recordings of the pulmonary artery diastolic pressure were displayed on ultraviolet paper and measured with a calibrated scale from a zero reference point. The pulmonary artery diastolic pressure was measured every fifteen minutes throughout the 24 hour period for each patient. For the purposes of analysis and display, values were normalised by expressing them as a ratio of the 24 hour mean pulmonary artery diastolic pressure for that patient.

Wilcoxon rank sum testing was performed on both the ratios and the absolute values.

Results

The table shows the 24 hour changes in pulmonary artery diastolic pressure for each group of patients. In each individual patient the mean pulmonary artery diastolic pressure over 24 hours was calculated and analysis was performed both on ratios and on absolute values. The statistical results were the same by both methods of calculation. For the purpose of clarity only the ratios are presented.

Normal controls—Figure 1 shows the diurnal variation in pulmonary artery diastolic pressure. Pulmonary artery diastolic pressure was significantly higher between midnight and 6 am than during the remainder of the 24 hours ($p < 0.01$).

Coronary artery disease—Figure 2 shows the diurnal variation in pulmonary artery diastolic pressure in the 18 patients with coronary artery disease. Again

Table *Twenty four hour median (range) pulmonary artery diastolic pressure for normal controls, patients with coronary artery disease, coronary artery spasm, and syndrome X*

	Number of patients	*24 hour pulmonary artery diastolic pressure (mm Hg)*
Normal controls	6	4·3 (2·1–7·6)
Coronary artery disease	18	8·1 (2·5–12·6)*
Variant angina	5	4·7 (3·3–16·3)
Syndrome X	6	2·9 (1·5–5·7)†

*Patients with coronary artery disease had a greater median pulmonary artery diastolic pressure than the controls ($p < 0.05$)

†Pulmonary artery diastolic pressure was lower in patients with syndrome X than in those with coronary artery disease ($p < 0.01$) but similar to that in controls.

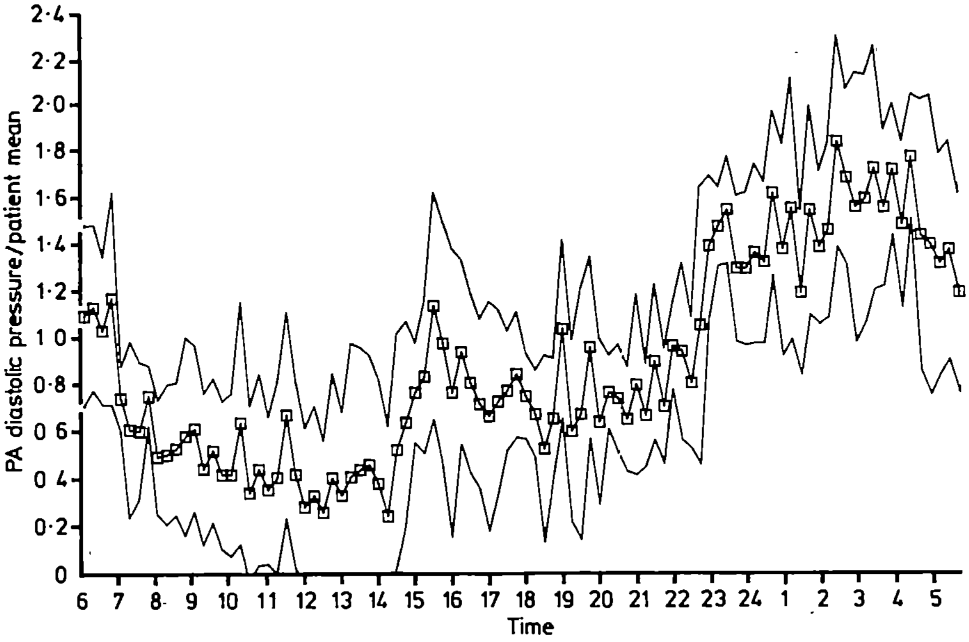

Fig 1 *Diurnal variation of pulmonary artery (PA) diastolic pressure in six normal subjects. Pulmonary artery diastolic pressure was significantly higher at night ($p < 0{\cdot}01$). Pulmonary artery diastolic pressure was measured throughout the 24 hour period for each patient and the values were normalised by expressing them as a ratio of the 24 hour mean pulmonary artery diastolic pressure for each patient. Mean pulmonary artery diastolic pressure (SD) is shown.*

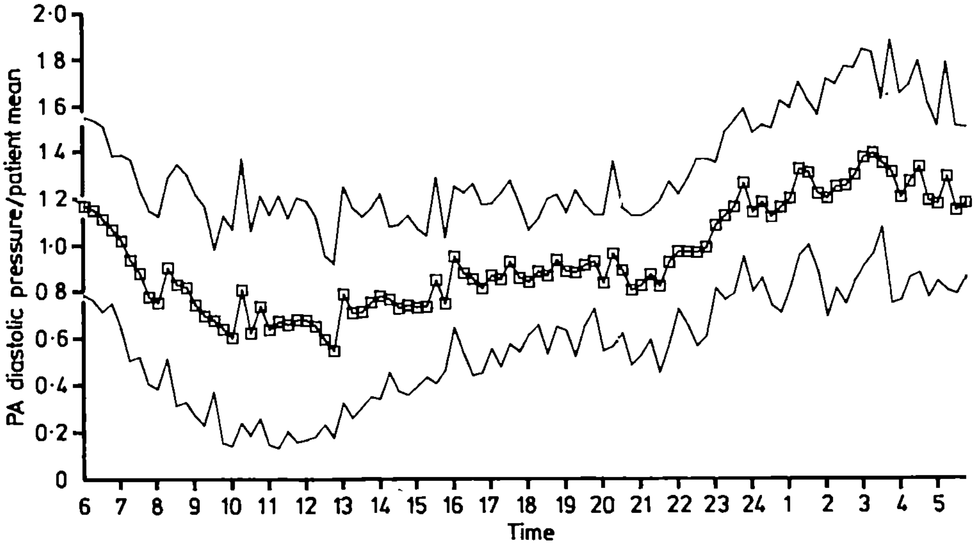

Fig 2 *Diurnal variation of pulmonary artery diastolic pressure in 18 patients with coronary artery disease. Pulmonary artery diastolic pressure was significantly higher at night ($p < 0{\cdot}01$). See legend to fig 1.*

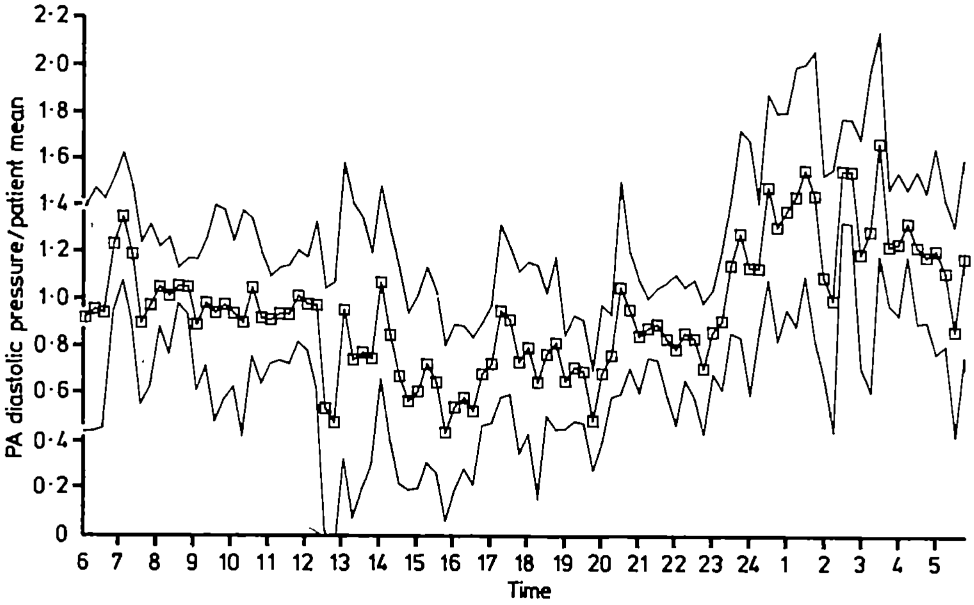

Fig 3 *Diurnal variation of pulmonary artery diastolic pressure in five patients with coronary artery spasm. Pulmonary artery diastolic pressure was significantly higher at night (p < 0·01). See legend to fig 1.*

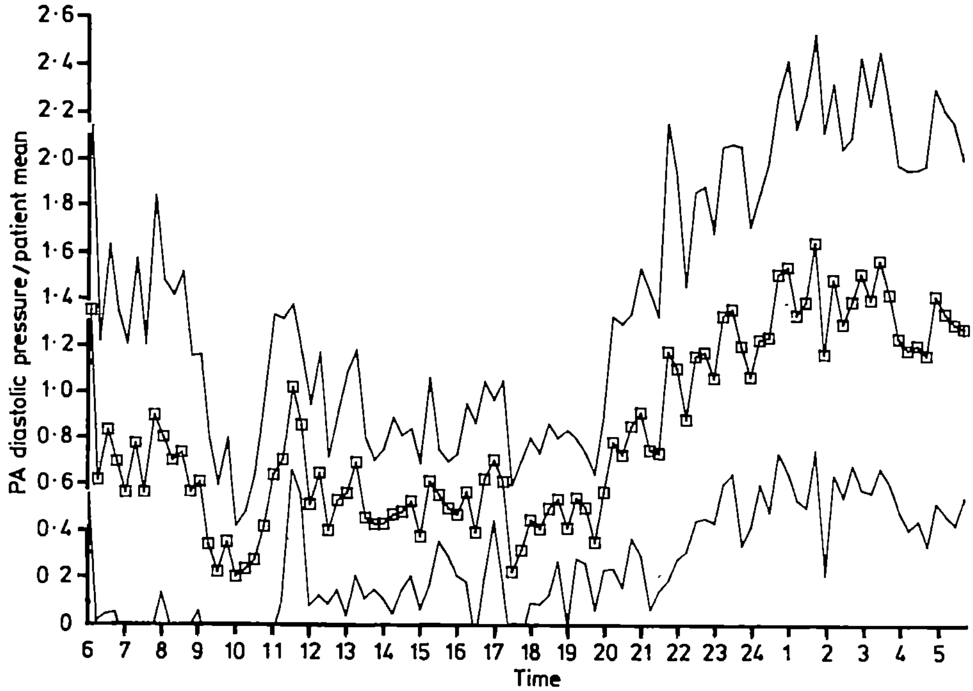

Fig 4 *Diurnal variation of pulmonary artery diastolic pressure in six patients with syndrome X. Pulmonary artery diastolic pressure was significantly higher at night (p < 0·01). See legend to fig 1.*

there was a significant rise in the pulmonary artery diastolic pressure between midnight and 6 am ($p < 0.01$). Ten of the total of 67 episodes of ST segment depression occurred during this six hour period. The 24 hour median pulmonary artery diastolic pressure in patients wth coronary artery disease (8·1 mm Hg, range 2·5–12·6) was greater than that in the control group (median 4·3 mm Hg, range 2·1–7·6) ($p < 0.05$).

Variant angina—Figure 3 shows the diurnal variation of pulmonary artery diastolic pressure in the five patients with variant angina. There was a significant rise in pulmonary artery diastolic pressure between the hours of midnight and 6 am ($p < 0.01$). In this group there were eight episodes of ST segment elevation between midnight and 6 am and six episodes at other times.

Syndrome X—Figure 4 shows the diurnal variation in pulmonary artery diastolic pressure in patients with syndrome X. There was a significant rise in pulmonary artery diastolic pressure between the hours of midnight and 6 am ($p < 0.01$). All episodes of ST segment depression occurred during the day when the patients were exercising. The 24 hour median pulmonary artery diastolic pressure was lower in patients with syndrome X (2·9 mm Hg, range 1·5–2·7) than those with coronary artery disease (median 8·1 mm Hg, range 2·5–12·6) ($p < 0.01$) but did not differ from that in the control group.

Discussion

Various mechanisms have been proposed to explain the precipitation of angina pectoris in patients with coronary artery disease. Angina pectoris is usually regarded as being the result of an increase in myocardial oxygen demand; however, recently alterations in coronary tone have been emphasised.[10 14]

At night patients with severe coronary disease often have an increase in heart rate before the onset of ST segment depression and the development of angina, possibly due to alterations in the phase of sleep associated with turning in bed, rapid eye movement sleep, and dreaming.[10 15–17] This increase in heart rate is, however, often less than that required to precipitate angina during the day. In such circumstances it has been suggested that an increase in coronary artery tone, possibly due to increased vagal activity, is also important.[14] Platelet aggregation will cause the release of thromboxane A_2, which is a potent vasoconstrictor; studies have shown a reduction in nocturnal myocardial ischaemia when platelet inhibitors are given.[18]

It has long been known that dilatation of the left ventricle[19] and increase in left ventricular filling pressure[20] are early events after myocardial ischaemia and will increase myocardial oxygen demand. To some extent this has been ignored as a mechanism of angina pectoris because of the difficulties of investigating this phenomenon. In previous studies of the haemodynamic changes in patients with angina fluid filled catheters have been used and the studies have been performed either in the catheter laboratory or coronary care unit.[20 21] The use of a transducer tipped catheter has avoided the problems of a fluid filled system, such as a low resonant frequency and the need for a transducer-perfusion unit with a constant zero reference point.[13 22 23]

In this study we have been able to measure the left ventricular filling pressure indirectly by measuring pulmonary artery diastolic pressure in ambulant subjects. Patients with coronary artery disease had a higher 24 hour median pulmonary artery diastolic pressure than the control group and patients with syndrome X.

For the first time a diurnal variation in the left ventricular filling pressure has been demonstrated. At night there were significant increases in left ventricular filling pressure in all groups of patients. The rise was less in patients with coronary artery disease than in the other groups though this difference is not significant. When a person lies down both pulmonary blood flow and pulmonary blood volume increase because of increased venous return.[24 25] It is therefore not surprising that we saw a diurnal rhythm in left ventricular filling pressure; however, the nocturnal rise occurred several hours after lying down. The rise in pulmonary artery diastolic pressure is unlikely to be due to myocardial ischaemia because it was seen in all groups. Episodes of nocturnal ischaemia are short lived whereas the rise in left ventricular filling pressure occurs gradually and lasts the whole night. The nocturnal rise in left ventricular filling pressure may be important in providing the setting for alterations in coronary tone or myocardial oxygen demand in patients with and without coronary artery spasm. It may also have important therapeutic implications because drugs that reduce left ventricular filling pressure such as nitrates may be particularly beneficial.

We thank the Clinical Research Committee of the National Heart and Chest Hospitals for financial support.

References

1 Millar-Craig MW, Bishop CN, Raftery ED. Circadian variation of blood pressure. *Lancet* 1978;i:795–7.

2 Boas EP, Weiss M. The heart rate during sleep. *JAMA*

1929;92:2162–8.

3 Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. *J Clin Endocrinol Metab* 1971;33:14–22.

4 Turton MB, Deegan T. Circadian variations of plasma catecholamine, cortisol and immunoreactive insulin concentrations in supine subjects. *Clin Chim Acta* 1974;55:389–97.

5 Muller JE, Stone PH, Turi ZG, *et al.* Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 1985;313:1315–22.

6 Agnoli A, Manfredi M, Mossut OL, Piccinelli A. Rapport entre les rythmes hemeronyctaux de la tension arterielle et sa pathogenie de l'insuffisance vasculaire cerebrale. *Rev Neurol (Paris)* 1975;131:597–606.

7 Quyyumi AA, Mockus L, Wright C, Fox KM. Morphology of ambulatory ST segment changes in patients with varying severity of coronary artery disease: investigation of the frequency of nocturnal ischaemia and coronary spasm. *Br Heart J* 1985;53:186–93.

8 Araki H, Koiwaya Y, Nakagaki O, Nakamura M. Diurnal variation of ST segment elevation and related arrhythmias on patients with variant angina: a study by ambulatory ECG monitoring. *Circulation* 1983;67:995–1000.

9 von Arnim T, Hofling B, Schreiber M. Characteristics of episodes of ST elevation or ST depression during ambulatory monitoring in patients subsequently undergoing coronary angiography. *Br Heart J* 1985;54:484–8.

10 Quyyumi AA, Wright CA, Mockus LJ, Fox KM. Mechanisms of nocturnal angina pectoris: importance of increased myocardial oxygen demand in patients with severe coronary artery disease. *Lancet* 1984;i:1207–9.

11 Maseri A, Severi S, De Nes M, *et al.* "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischaemia: pathogenic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. *Am J Cardiol* 1978;42:1019–35.

12 Heberden W. *Commentaries on the history and cure of diseases*. London: Payne, 1802.

13 Levy RD, Cunningham D, Shapiro LM, Wright C, Mockus L, Fox KM. Continuous ambulatory pulmonary artery pressure monitoring: a new method using a transducer-tipped catheter and a simple recording system. *Br Heart J* 1986;55:336–43.

14 Chierchia S, Brunelli C, Simonetti I, Lazzari M, Maseri A. Sequence of events in angina at rest: primary reduction in coronary flow. *Circulation* 1980;61:759–68.

15 Quyyumi AA, Efthimiou J, Bealing AL, *et al.* Mechanisms of rest angina evaluated during sleep [Abstract]. *Br Heart J* 1984;51:693.

16 Maurao S, Harumi K, Katayama S, *et al.* All-night polygraphic studies of nocturnal angina pectoris. *Jpn Heart J* 1972;13:295–306.

17 Nowlin JB, Troyer WG, Collins WS, *et al.* The association of nocturnal angina pectoris with dreaming. *Ann Intern Med* 1965;63:1040–6.

18 Fox KM, Jonathan A, Selwyn AP. The effects of platelet inhibition on myocardial ischaemia. *Lancet* 1982;ii:727–30.

19 Nichols AB, Strauss HW, Moore RH, *et al.* Acute changes in cardiopulmonary blood volume during upright exercise stress testing in patients with coronary heart disease. *Circulation* 1979;60:520–30.

20 Chierchia S, Lazzari M, Freedman SB, Brunelli C, Maseri A. Impairment of myocardial perfusion and function during painless myocardial ischaemia. *J Am Coll Cardiol* 1983;1:924–30.

21 Friesinger GC, Conti CHR, Pitt B. Observation on left ventricular pressure during angina pectoris [Abstract]. *Circulation* 1967;36(suppl 11):115.

22 Ikram H, Richards AM, Hamilton EJ, Nicholls MG. Continuous recording of pulmonary artery pressure in unrestricted subjects. *Br Heart J* 1984;51:421–6.

23 Saumaraz RC. Continuous recording of pulmonary artery pressure [Letter]. *Br Heart J* 1985;53:581–3.

24 Weissler AM, McGraw BH, Warren JV. Pulmonary blood volume determined by a radioactive tracer technique. *J Appl Physiol* 1959;14:531–4.

25 Stead EA Jr, Warren JV, Merill AJ, Brannon ES. The cardiac output in male subjects as measured by the technique of right atrial catheterisation. Normal values with observations on the effect of anxiety and tilting. *J Clin Invest* 1945;24:326–31.

Br Heart J 1987;57:154–60

Left ventricular function at similar heart rates during tachycardia induced by exercise and atrial pacing: an echocardiographic study

LUC A PIÉRARD,* PATRICK W SERRUYS, JOS ROELANDT,
RICHARD S MELTZER†

From the Department of Clinical Echocardiography, Thoraxcenter, Erasmus University and Academic Hospital Dijkzigt, Rotterdam, the Netherlands

SUMMARY M mode echocardiography was used in 10 normal subjects to study left ventricular dimension and function variables at identical heart rates during tachycardia induced by supine bicycle exercise or atrial pacing. Echocardiographic data were analysed independently by two observers. The maximum heart rate reached during atrial pacing was lower (mean (1SD) 148 (17) beats/min) than that reached during exercise (mean (1SD) 167 (14) beats/min). The left ventricular end diastolic dimension was greater before supine exercise than before atrial pacing, probably as a result of leg raising. At each graded exercise step the end diastolic dimension remained greater than during atrial pacing and the differences became progressively greater with increasing heart rates. The left ventricular end systolic dimension was not significantly different at each step during the two stresses. During recovery the end systolic dimension was significantly smaller after exercise than at corresponding heart rates induced by atrial pacing. Left ventricular function indices—fractional shortening and peak rates of left ventricular systolic and diastolic dimensional change—were significantly higher during exercise than during atrial pacing and the differences increased with heart rate.

It is concluded that (*a*) the intervention used to change heart rate has an important effect on M mode echocardiographic left ventricular dimensions; (*b*) indices of left ventricular performance increase progressively during exercise and differ from those measured at the same heart rate during atrial pacing; (*c*) it is important to consider heart rate, stroke volume, and loading conditions when reference values are used and when the effects of a particular stress are to be interpreted.

Adaptation of the cardiovascular system to dynamic exercise results from integrated mechanisms including an increase in heart rate and contractility, changes in preload and afterload, and a decrease in peripheral resistance.[1] Echocardiography permits non-invasive assessment of left ventricular size and function in subjects at rest.[2 3] Exercise echocardiography has the important advantage of allowing continuous measurement of left ventricular function variables before, during, and immediately after exercise. Different types of stress and exercise have been studied echocardiographically, including isometric exercise[4]; handgrip[5]; and bicycle ergometer exercise in supine,[5 6] semisupine,[7 8] sitting,[9] and upright positions.[5 10 11]

M mode echocardiographic variables of the left ventricle are known to vary with heart rate,[12 13] but differences due to separate interventions have not been compared in the same subjects. The aim of the present study was to analyse left ventricular function at identical heart rates induced by supine bicycle exercise and atrial pacing.

Requests for reprints to Dr Luc A Piérard, Université de Liège, Service de Cardiologie, Boulevard de la Constitution 59, B-4020 Liège, Belgium.

Present addresses: *Department of Cardiology, Institute of Medicine, University Hospital, Liège, Belgium; †University of Rochester Medical Center, Rochester, New York 14642, USA.

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Subjects and methods

STUDY POPULATION

We studied ten healthy volunteers (medical students; mean age 24, range 20–41) with resting M mode echocardiograms of excellent quality. All had a normal history, physical examination, resting and exercise electrocardiogram, and chest *x* ray. We obtained informed consent from all of them. The subjects were not required to fast before the tests; hence studies were performed with normal volume loading of the left ventricle.

BICYCLE EXERCISE STRESS TEST

The 10 subjects lay supine on a table in a slightly left lateral position and were fixed at the shoulder level. They pedalled a bicycle ergometer at 60 revolutions/min. The initial workload was 50 W for three minutes; this was increased by 25 W every three minutes until the subject was exhausted. The mean (1 SD) duration of exercise was 22 (3) minutes and the maximal workload was 212 (30) W.

M mode echocardiograms were recorded before exercise with the subject's feet elevated in the cycling position, at the end of each three minute exercise period, and every minute during recovery. The heart rate was measured on the simultaneously recorded electrocardiogram. Brachial blood pressure was measured every minute with a mercury sphygmomanometer.

ATRIAL PACING STRESS TEST

The day after the exercise test, at nearly the same time, the 10 subjects were studied in the catheterisation laboratory. An electrode catheter (5F bipolar) was inserted into the right atrium via a left antecubital vein. The subjects rested until heart rate and blood pressure were stable. M mode echocardiograms were then recorded with the subject in the supine and slight left lateral decubitus position—at rest and after a steady state period of 60 seconds of atrial pacing—at the same heart rates as those achieved at the end of each step of the exercise test. Atrial pacing was stopped in each subject when a 1:1 atrioventricular conduction failed. Arterial blood pressure was measured with a mercury sphygmomanometer during the recording of each echocardiogram.

ECHOCARDIOGRAPHIC STUDY AND ANALYSIS

M mode echocardiography was performed with a 2.25 MHz transducer placed at the left parasternal border in the same position that was marked during exercise and atrial pacing stress. The recordings were made at 50 mm/second paper speed during end expiration. We took care to record left ventricular echocardiograms below the tips of mitral valve leaflets with clearly defined echoes of the interventricular septum and the posterior wall endocardium and epicardium.

The echocardiograms were obtained at rest; at the end of each step of exercise test; at 2, 3, and 5 minutes during recovery; and at identical heart rates induced by atrial pacing. The tracings were analysed on a digitising tablet connected to a PDP 11 digital computer.[14] Three consecutive beats were independently traced by two observers who used the leading edge to leading edge method. The results were averaged to obtain a single value in order to avoid beat to beat variability.

The following measurements of the left ventricle were made: left ventricular end diastolic diameter (EDD) (in mm) at the onset of the QRS complex; left ventricular end systolic diameter (ESD) (mm) defined as the minimum diameter in systole; and fractional shortening

$$\left(\text{FS}\,\% = \frac{(\text{EDD} - \text{ESD})}{\text{EDD}} \times 100\right).$$

The following indices of left ventricular function

Table *Reproducibility of digitisation during exercise: interobserver variability*

	Observer				*2 SD*
	1	*2*	%*	*R*†	*limit*
Heart rate (beats/min)	119 (25)	119 (27)	0·6	0·87	8·9
LVEDD (mm)	57·2 (6·0)	57·3 (5·8)	0·2	0·98	1·57
LVESD (mm)	37·4 (4·8)	37·8 (4·7)	0·9	0·98	1·5
Fractional shortening (%)	34 (4)	34 (4)	1·36	0·94	2·03
VCF/EDD (s^{-1})	0·92 (0·19)	0·93 (0·18)	1·5	0·71	0·2
Max decrease dD/dt/EDD	2·75 (0·52)	2·70 (0·46)	1·8	0·88	0·36
Max increase dD/dt/EDD	4·96 (1·19)	4·86 (1·08)	2	0·84	0·91

LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; VCF/EDD, velocity of circumferential fibre shortening standardised for end diastolic dimension; max decrease dD/dt/EDD, maximum rate of decrease in left ventricular dimension standardised for end diastolic dimension; max increase dD/dt/EDD, maximum rate of increase in left ventricular dimension standardised for end diastolic dimension.

*Percentage difference between means.

†Correlation coefficient.

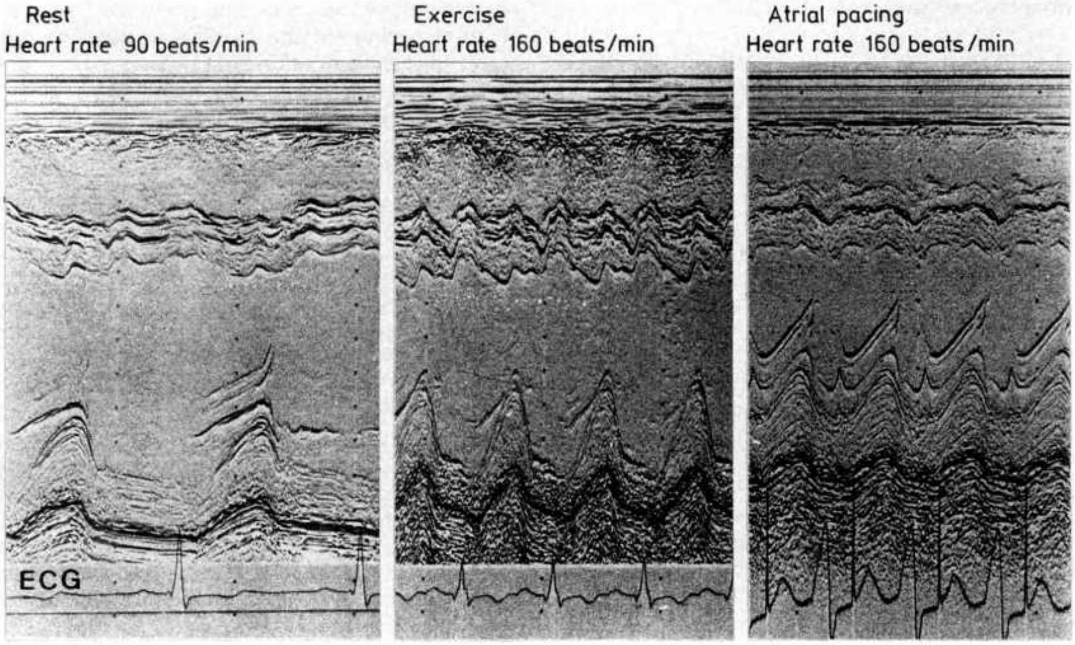

Fig 1 *M mode echocardiograms of the left ventricle obtained at rest and at the maximum comparable heart rate during exercise and atrial pacing. The 1 cm calibration is similar in the three panels. There was a reduction in left ventricular end systolic dimension during exercise and a reduction in both left ventricular end diastolic and end systolic dimensions during atrial pacing.*

(standardised for end diastolic dimension) were determined: mean velocity of circumferential fibre shortening (VCF/EDD, s^{-1}), peak rate of decrease in left ventricular diameter (maximum systolic dD/dt/EDD, s^{-1}), and peak rate of increase in left ventricular diameter (maximum diastolic dD/dt/EDD, s^{-1}).

STATISTICAL ANALYSIS

For each variable, measurements obtained at each step during the exercise test were compared with those made at identical heart rates induced by atrial pacing. Student's *t* test for paired data was used. Differences were regarded as significant when $p < 0{\cdot}05$.

Results

REPRODUCIBILITY OF DIGITISATION OF EXERCISE ECHOCARDIOGRAMS

For each variable measured during exercise we regarded the mean value of three consecutive cardiac cycles obtained by digitisation as an individual determination. Interobserver variability was assessed by calculation of the percentage difference between the means of the two observers (table). Variance between the two observers was small for all variables, the maximum being 2% for normalised peak rate of increase in diameter, a derived index. The correlation of the results between the two independent observers was highly significant (table).

HEART RATE

In two subjects 1:1 atrioventricular conduction failed during atrial pacing at low heart rates and thus we could not compare the results with exercise after the first step. These patients were excluded from further analysis and we compared paired variables at similar heart rates in the eight remaining subjects.

Resting heart rates were similar before exercise (73 (13) beats/minute) and before atrial pacing (73 (15) beats/minute). During exercise we obtained adequate tracings for digitisation up to maximal heart rates (167 (14) beats/minute). The mean maximal heart rate reached during atrial pacing (148 (17) beats/minute) was lower because the Wenckebach phenomenon occurred at heart rates lower than those achieved during exercise. Figure 1 shows representative echocardiograms obtained at rest and at the maximal heart rates achieved during exercise and atrial pacing.

SYSTOLIC ARTERIAL BLOOD PRESSURE

Systolic arterial blood pressure was not significantly different before exercise (138 (5) mm Hg), and before atrial pacing (130 (11) mm Hg). It increased to 191 (14) mm Hg at maximal exercise level ($p < 0{\cdot}01$) and decreased slightly, but not significantly, at maximal atrial pacing induced tachycardia (123 (14) mm Hg).

LEFT VENTRICULAR CAVITY DIMENSIONS

Figure 2a shows the effects of supine exercise and atrial pacing induced tachycardia on left ventricular end diastolic dimension. At rest the end diastolic dimension was greater before exercise than before atrial pacing ($p < 0{\cdot}05$). The end diastolic dimension remained fairly constant during exercise and decreased during atrial pacing. At each step of the two stress tests the end diastolic dimension was greater during exercise than during atrial pacing and the differences increased progressively. During recovery the differences decreased progressively and after five minutes end diastolic dimension was similar to the value obtained at the corresponding heart rate induced by atrial pacing. During recovery subjects kept their feet up on the table. Figure 2b shows the influence of exercise and atrial pacing on left ventricular end systolic dimension. End systolic dimension decreased slightly during both exercise and atrial pacing and no significant differences were seen between the two stress tests at any level. During recovery left ventricular end systolic dimension was significantly smaller after exercise than at corresponding heart rates produced by atrial pacing ($p < 0{\cdot}05$).

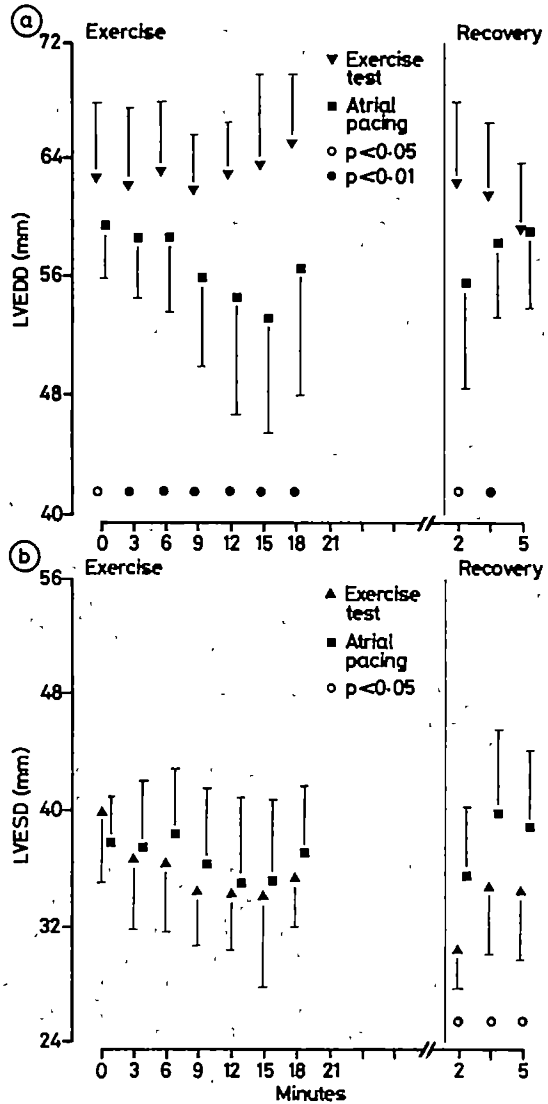

Fig 2 *Measurements of (a) left ventricular end diastolic dimension (LVEDD) and (b) left ventricular end systolic dimension (LVESD) at each step of exercise and recovery and at identical heart rates induced by atrial pacing. Mean (1SD) values of all subjects are indicated.*

INDICES OF LEFT VENTRICULAR FUNCTION

Figure 3a shows the effects of exercise and atrial pacing on fractional shortening. Fractional shortening values were similar before exercise and atrial pacing. This variable remained constant during atrial pacing and increased progressively during exercise. This difference was significant at all levels of stress. After five minutes of recovery from exercise, fractional shortening values remained higher than at corresponding heart rates produced by atrial pacing.

Figures 3b and 3c show the effects of exercise and atrial pacing on the rate of left ventricular dimensional decrease (maximum systolic dD/dt/EDD) and increase (maximum diastolic dD/dt/EDD). Both indices showed a tendency to increase slightly during atrial pacing (NS) and a progressive and greater significant increase during exercise ($p < 0{\cdot}0001$ at all steps of exercise). The difference between these values during the two stresses was statistically significant.

Discussion

Previous studies have shown that M mode echocardiography is an accurate and reproducible method for measuring left ventricular cavity dimensions at rest.[15-17] Interest in exercise echocardiography is increasing but the technique is difficult to perform, especially with the subject in the upright position.[10] In this study we obtained good quality M mode echocardiograms during maximal

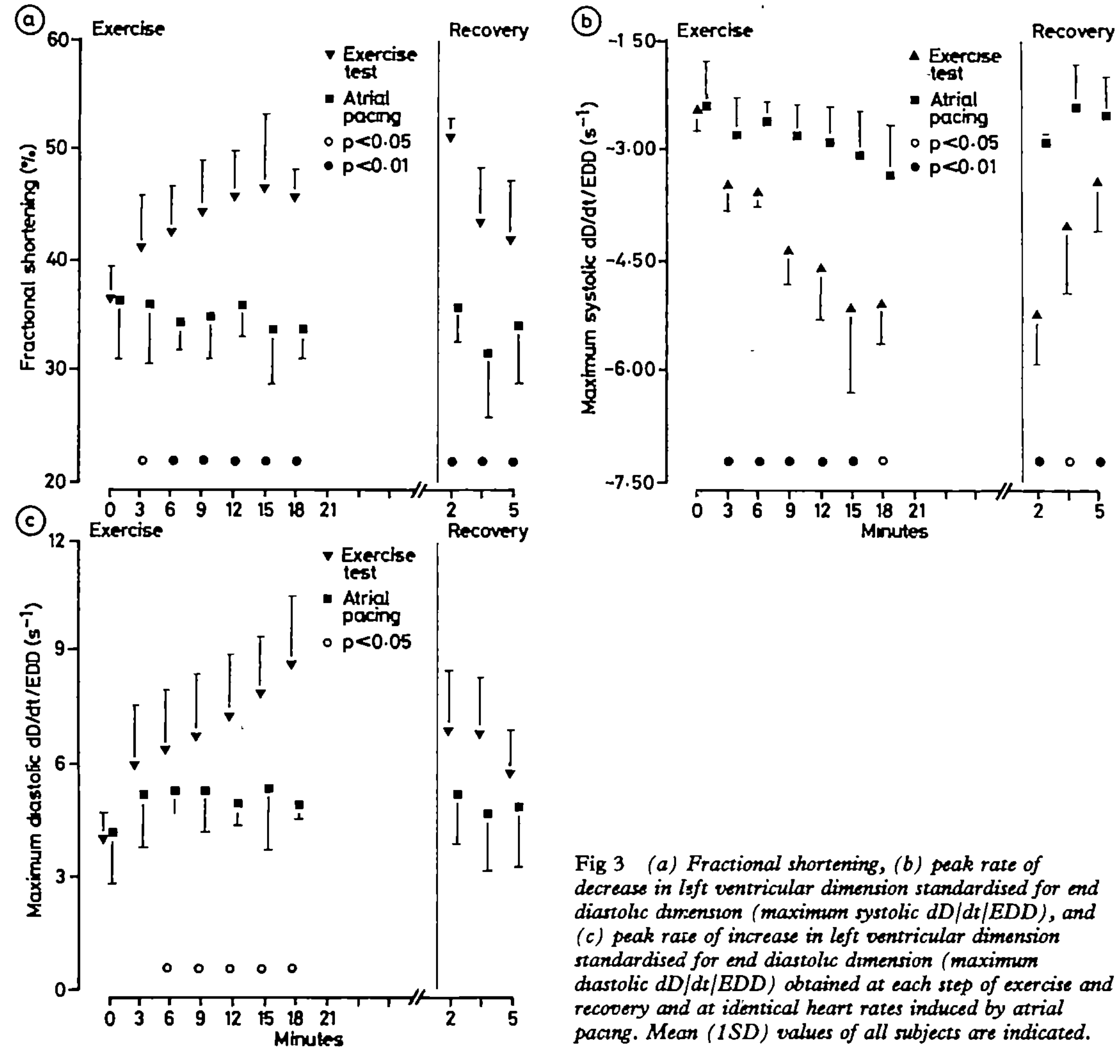

Fig 3 *(a) Fractional shortening, (b) peak rate of decrease in left ventricular dimension standardised for end diastolic dimension (maximum systolic dD/dt/EDD), and (c) peak rate of increase in left ventricular dimension standardised for end diastolic dimension (maximum diastolic dD/dt/EDD) obtained at each step of exercise and recovery and at identical heart rates induced by atrial pacing. Mean (1SD) values of all subjects are indicated.*

supine exercise tests in young selected healthy subjects.

LEFT VENTRICULAR DIMENSIONS

Most studies in exercising dogs have shown an increasing left ventricular end diastolic dimension.[18–20] Several techniques have been used to measure left ventricular dimension change during exercise in man: M mode echocardiography,[5–10] myocardial markers,[21–24] left ventricular angiography,[25 26] and radionuclide angiography.[11 27–30] Radionuclide studies performed in upright subjects have demonstrated an increase in left ventricular end diastolic dimension[11 28 29] whereas Crawford *et al* using M mode echocardiography did not observe any change during moderate upright exercise.[5] Data on left ventricular dimension changes during exercise in the supine position are even more conflicting. An increase in left ventricular end diastolic volume was demonstrated by Poliner *et al* using radionuclide techniques[29] and this was confirmed by Sharma *et al* using cineangiography.[26] Left ventricular end diastolic volume remained unchanged in Gorlin *et al's* angiographic study[25] and in that of Slutsky *et al* who used radionuclide angiography.[28] Weiss *et al* found an increase in echocardiographic end diastolic dimension during maximal semisupine exercise.[7] In most echocardiographic studies, however, no significant changes were found in end diastolic dimension during supine exercise.[5,6,8] Studies with myocardial markers showed that the end diastolic dimension decreased[21,31] or remained unchanged.[23]

In the denervated heart of cardiac transplant recipients an early increase during exercise has been demonstrated.[24] The findings of most of these studies, and particularly those using echocardiography and radionuclide techniques, have been interpreted on the basis of the presence or absence of a Frank-Starling mechanism without considering the influence of heart rate. Our findings suggest that leg elevation just before supine exercise significantly increases left ventricular end diastolic dimension. Because the feet were raised at rest just before exercise, end diastolic dimension was greater than before atrial pacing when the feet were horizontal. The mean difference of 3·2 mm (5·2%) was outside the 95% confidence interval of temporal variability in serial echocardiograms and must be regarded as significant.[32] This increase in preload was not accompanied by an inotropic effect since all the indices of left ventricular function—fractional shortening, mean velocity of circumferential fibre shortening, and peak rate of decrease in diameter—were not significantly different before the two tests were started. We observed that at any given heart rate during stress, left ventricular end diastolic dimensions were greater during exercise than during atrial pacing induced tachycardia. These observations accord with those of Sonnenblick *et al* who studied patients by means of myocardial markers after cardiac operations.[22] An increase in heart rate tends to decrease end diastolic dimension whereas increased venous return has the opposite effect. Thus the maintenance of end diastolic dimension during supine exercise suggests that the Frank-Starling mechanism is active in the cardiac response to exercise.

Though most of the previous studies have shown a decrease in end systolic dimension during both supine and upright exercise,[5,6,8,20,23,25,26] indicating increased emptying of the left ventricle, others have not confirmed these findings.[7,19] Poliner *et al* found no change in end systolic volume in the supine position, but they did report a significant decrease during upright exercise.[29] Our results show that there is a trend towards a decrease in end systolic dimension during exercise, but the measurements are not significantly different from those made at corresponding heart rates induced by atrial pacing. During recovery after exercise the end systolic dimension was smaller than at similar heart rates during atrial pacing. These findings are in accord with increased left ventricular emptying during recovery caused by persistently high catecholamine concentration and a decreased afterload due to peripheral vasodilatation.

LEFT VENTRICULAR FUNCTION

The positive inotropic effect of increasing the frequency of contraction has been described by many investigators.[22,33-38] In our study fractional shortening remained constant during atrial pacing and there was a tendency to a slight not statistically significant increase in mean normalised velocity of circumferential fibre shortening and peak rate of decrease in left ventricular diameter. These results accord with those reported by DeMaria *et al.*[12]

During exercise, however, there was a progressive increase in fractional shortening, normalised velocity of circumferential fibre shortening, and peak rate of decrease in left ventricular diameter. Thus it appears that the tachycardia per se is not the major factor in the increase of contractility during exercise.

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References

1 Braunwald E, Ross J Jr, Sonnenblick EH. Circulatory adjustments during exercise. In: Braunwald E, Ross J Jr, Sonnenblick EH, eds. *Mechanisms of contraction of the normal and failing heart.* 2nd ed. Boston: Little, Brown, 1976:292–308.

2 Fortuin NJ, Hood WP, Sherman ME, Craige E. Determination of left ventricular volumes by ultrasound. *Circulation* 1971;44:575–84.

3 Quinones MA, Gaasch WH, Alexander JK. Echocardiographic assessment of left ventricular function with special reference to normalized velocities. *Circulation* 1974;50:42–51.

4 Laird WP, Fixler DE, Huffines FD. Cardiovascular response to isometric exercise in normal adolescents. *Circulation* 1979;59:651–61.

5 Crawford MH, White DH, Amon KW. Echocardiographic evaluation of left ventricular size and performance during handgrip and supine and upright bicycle exercise. *Circulation* 1979;59:1188–96.

6 Stein RA, Michielli D, Fox EL, Krasnow N. Continuous ventricular dimensions in man during supine exercise and recovery. *Am J Cardiol* 1978;41:655–60

7 Weiss JL, Weisfeldt ML, Mason SJ, Garrison JB, Livengood SV, Fortuin NJ. Evidence of Frank-Starling effect in man during severe semisupine exercise. *Circulation* 1979;59:655–61.

8 Andersen K, Vik-Mo H. Role of the Frank-Starling mechanism during maximal semisupine exercise after oral atenolol. *Br Heart J* 1982;48:149–55.

9 Corallo S, Broso GP, Sega R, *et al.* Value and limits of exercise echocardiography in normal and pathological conditions. In: Kuriak A, Kratochwil A, eds.

Recent advances in ultrasound diagnosis 3. Amsterdam: Excerpta Medica, 1981:428–32.

10 Goldstein RE, Bennett ED, Leech GL. Effect of glyceryl trinitrate on echocardiographic left ventricular dimensions during exercise in the upright position. *Br Heart J* 1979;42:245–54.

11 Wijns W, Melin JA, Vanbutsele RJ, *et al.* Assessment of right and left ventricular volumes during upright exercise in normal men. *Eur Heart J* 1982;3:529–36.

12 DeMaria AN, Neumann A, Schubart PJ, Lee G, Mason DT. Systematic correlation of cardiac chamber size and ventricular performance determined with echocardiography and alterations in heart rate in normal persons. *Am J Cardiol* 1979;43:1–9.

13 Roelandt J, Van Dorp WG, Hugenholtz PG. Continuous analysis of ventricular function during atrial pacing using echocardiography [Abstract]. *Circulation* 1975;52(suppl II):233.

14 Vogel JA, Van Zwieten G, Bom N. Data processing of time-motion information in echocardiography. In: Bom N, ed. *Echocardiology*. The Hague: Martinus Nijhoff, 1977:335–47.

15 Popp RL, Filly K, Brown OR, Harrison DC. Effect of transducer placement on echocardiographic measurement of left ventricular dimensions. *Am J Cardiol* 1975;35:537–40.

16 Ladipo GOA, Dunn FG, Pringle TH, Bastian B, Lawrie TDV. Serial measurements of left ventricular dimensions by echocardiography: assessment of week-to-week, inter- and intraobserver variability in normal subjects and patients with valvular heart disease. *Br Heart J* 1980;44:284–9.

17 Felner JM, Blumenstein BA, Schlant RC, *et al.* Source of variability in echocardiographic measurements. *Am J Cardiol* 1980;45:995–1004.

18 Wilson MF. Left ventricular diameter, posture and exercise. *Circ Res* 1962;11:90–7.

19 Horwitz L, Atkins J, Leshin SJ. Role of the Frank-Starling mechanism in exercise. *Circ Res* 1972; 31:868–74.

20 Vatner S, Franklin D, Higgins C, Patrick T, Braunwald E. Left ventricular response to severe exertion in untethered dogs. *J Clin Invest* 1972;51:3052–9.

21 Braunwald E, Goldblatt A, Harrison DC, Mason DT. Studies on cardiac dimensions in intact, unanesthetized man. *Circ Res* 1963;13:460–7.

22 Sonnenblick EH, Braunwald E, Williams JF Jr, Glick G. Effects of exercise on myocardial force-velocity relations in intact unanesthetized man: relative roles of changes in heart rate, sympathetic activity and ventricular dimensions. *J Clin Invest* 1965;44:2051–62.

23 McLaughlin PR, Kleiman JH, Martin RP, *et al.* The effect of exercise and atrial pacing on left ventricular volume and contractility in patients with innervated and denervated hearts. *Circulation* 1978;58:476–83.

24 Pope SE, Stinson EB, Daughters GT, Schroeder JS, Ingels NB, Alderman EL. Exercise response of the denervated heart in long-term cardiac transplant recipients. *Am J Cardiol* 1980;46:213–8.

25 Gorlin R, Cohen L, Elliott W, Klein M, Lane F. Effect of supine exercise on left ventricular volume and oxygen consumption in man. *Circulation* 1965;32:361–6.

26 Sharma B, Goodwin JF, Raphael MJ, Steiner RE, Rainbow RG, Taylor SH. Left ventricular angiography on exercise: a new method of assessing left ventricular function in ischaemic heart disease. *Br Heart J* 1976;38:59–70.

27 Rerych R, Scholz P, Newman G, Sabiston D, Jones R. Cardiac function at rest and during exercise in normals and patients with coronary heart disease. *Ann Surg* 1978;187:449–60.

28 Slutsky R, Karliner J, Ricci D, *et al.* Response of left ventricular volume to exercise in man assessed by radionuclide equilibrium angiography. *Circulation* 1979;60:565–71.

29 Poliner LR, Dehmer GJ, Lewis SE, Parkey RW, Blomqvist CG, Willerson JT. Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions. *Circulation* 1980;62:528–34.

30 Upton M, Rerych S, Roeback JR Jr, *et al.* Effect of brief and prolonged exercise on left ventricular function. *Am J Cardiol* 1980;45:1154–60.

31 Braunwald E, Goldblatt A, Harrison D, Mason D. Studies on cardiac dimensions in intact, unanesthetized man. *Circ Res* 1963;13:448–56.

32 Clark RD, Korcuska K, Cohn K. Serial echocardiographic evaluation of left ventricular function in valvular disease, including reproducibility guidelines for serial studies. *Circulation* 1980;62:564–75.

33 Bowditch HP. Uber die Eigenthumlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens Ziegen. *Arb Physiologischem Anstalt Leipzig* 1871;6:139–52.

34 Dale AS. The staircase phenomenon in ventricular muscle. *J Physiol (Lond)* 1932;75:1–6.

35 Blinks JR, Koch-Weser J. Analysis of the effects of changes in rate and rhythm upon myocardial contractility. *J Pharmacol Exp Ther* 1961;134:373–89.

36 Boerth RC, Covell JW, Pool PE, Ross J. Increased myocardial oxygen consumption and contractile state associated with increased heart rate in dogs. *Circ Res* 1969;24:725–34.

37 Ricci D, Orlick A, Alderman E. Role of tachycardia as an inotropic stimulus in man. *J Clin Invest* 1979;63:695–702.

38 Roelandt JR, Meester GT, Hugenholtz PG. Vmax and dD/dt/kPmax in patients with coronary artery disease during atrial pacing [Abstract]. *Circulation* 1971; 44(suppl 2):96.

Br Heart J 1987;57:161–7

Pulsed Doppler echocardiographic evaluation of neonatal circulatory changes

HIROHIKO SHIRAISHI,* MASAYOSHI YANAGISAWA

From the Department of Paediatrics, Jichi Medical School, Tochigi, Japan

SUMMARY Pulsed Doppler echocardiograms were obtained from 42 normal fullterm neonates at <12 hours (20 subjects), 4 days (20 subjects), and 33 days (12 subjects). The acceleration time of the flow velocity and ventricular systolic time intervals were measured on recordings obtained at the right and left ventricular outflow tract, and the patency of the ductus arteriosus was evaluated by the flow at the pulmonary end of the ductus. The flow velocity pattern of the right ventricular outflow tract changed from a triangular shape with a peak velocity in early systole in the younger age groups to a dome-like contour with a peak velocity in mid-systole; thus the ratio of mean acceleration time to right ventricular ejection time increased with age. The flow velocity pattern of the left ventricular outflow tract was triangular in all age groups, and the ratio of mean acceleration time to left ventricular ejection time showed no significant change with age. The right ventricular pre-ejection period shortened and the right ventricular ejection time lengthened with age; thus the ratio of mean right ventricular pre-ejection period to right ventricular ejection time decreased with age. The left ventricular systolic time intervals showed no significant change with age. The ductus arteriosus was patent in all subjects who were less than 12 hours old but was closed in the older neonates.

Pulsed Doppler echocardiography is a valuable method of evaluating pulmonary vascular bed in the early neonatal period.

Soon after birth the ductus arteriosus and foramen ovale close and there are considerable falls in pulmonary vascular resistance and pulmonary artery pressure.[1] It would be useful to have a reliable noninvasive method of evaluating these changes. Pulsed Doppler echocardiography has been used to assess blood flow in the heart and great vessels noninvasively, and it has various clinical applications including detection of valvular stenosis or insufficiency and shunt lesions.[2 3] The flow velocity pattern of the right ventricular outflow tract has been shown to be useful in assessing the pulmonary vascular resistance and diastolic pressure of the pulmonary artery in patients with congenital heart disease.[4 5]

To test the hypothesis that the flow pattern of the right ventricular outflow tract might reflect the decreasing pulmonary vascular resistance and diastolic pressure of the pulmonary artery in the early neonatal period we studied the normal flow patterns of the right and left ventricular outflow tracts in the first month of life by pulsed Doppler echocardiography.

Subjects and methods

We examined 42 neonates and infants (estimated gestation 37–41 weeks): 20 <12 hours old (0 day old), 20 3–9 days old (4 day old), and 12 28–37 days old (1 month old). Ten neonates were examined twice. All infants had uneventful perinatal histories and were normal by physical examinations and by cross sectional echocardiograms. The heart rates of the infants ranged from 90 to 160 beats/min at the time of examination and neither arrhythmia nor conduction abnormalities were noted. Informed parental consent was obtained for all subjects before examination.

For pulsed Doppler echocardiography we used an

Requests for reprints to Dr Hirohiko Shiraishi, Department of Paediatrics, Jichi Medical School, Minamikawachi, Tochigi, 329-04, Japan.

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Aloka SSD-720 compound ultrasound diagnostic device and a pulsed Doppler transducer (Aloka ASU-32-5), with a carrier frequency of 5·0 MHz and pulse repetition frequency of 8·0 KHz. The length of the sample volume was 2 mm. Doppler signals were analysed by fast Fourier transform with an Aloka UGR-23 pulsed Doppler unit, displayed in the form of frequency spectrum, and recorded with an Aloka SSZ-95 strip chart recorder at a paper speed of 100 mm/s together with an electrocardiogram and M mode echocardiogram on which the depth of the sample volume was marked. Flow away from the transducer was displayed below the baseline and flow towards the transducer was displayed above the baseline. The time lag in the sample and frequency analysis of Doppler signals has been estimated to be 22–28 ms.[6 7]

The transducer was placed at the intercostal space of the left lower sternal border and at the apex to obtain clear parasternal short axis and apical long axis images. The sample volume was then moved to just below the semilunar valves at each ventricular outflow tract and then to the pulmonary end of the ductus. Care was taken to align the ultrasonic Doppler beam with the flow in each ventricular outflow tract. All infants were examined while they were sleeping or resting quietly.

We measured three variables on the spectral records of the pulsed Doppler echocardiograms of the right and left ventricular outflow tracts: these were the pre-ejection period (PEP), which was defined as the time from the Q wave of the electrocardiogram to the onset of the ejection flow; the acceleration time (AcT), which was defined as the time from the onset of the flow to the peak velocity; and the ejection time (ET), which was defined as the time from the onset of the flow to the end of the flow (fig 1). Five sequential complexes were measured

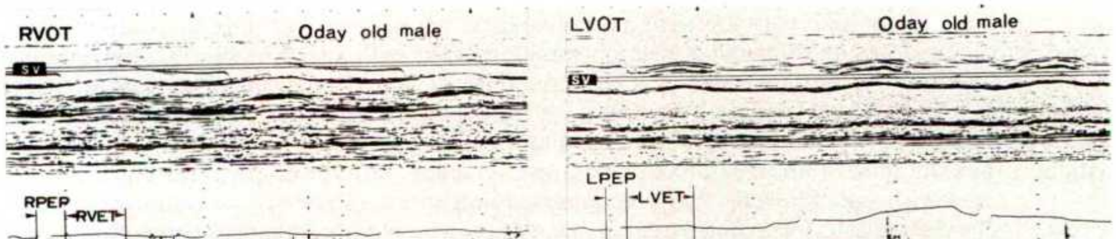

Fig 1 *Pulsed Doppler echocardiogram obtained at the right ventricular outflow tract (RVOT) and left ventricular outflow tract (LVOT) 0 and 5 days after birth. (a) The right ventricular outflow tract flow pattern changed from a triangular shape with a peak velocity in early systole (top) to a dome shape with a peak velocity in mid-systole (bottom). (b) The left ventricular outflow tract flow pattern was triangular with a peak velocity in early systole and did not change with increasing age. RPEP, right pre-ejection period; RVET, right ventricular ejection time; AcT, acceleration time; LPEP, left pre-ejection period; LVET, left ventricular ejection time; SV, sample volume.*

Table *Right and left systolic time intervals and AcT:ET ratios at three ages (mean (SD))*

	0 day (2–12 hrs) *(n = 20, M/F = 12/8)*	*4 day (3–9 days)* *(n = 20, M/F = 11/9)*	*1 month (28–37 days)* *(n = 12, M/F = 3/9)*
Heart rate (beats/min)	121 (11)	117 (14)	142 (15)*
RPEP (ms)	93·8 (14·7)	72·1 (11·9)*	64·3 (5·8)*
AcT (ms)	68·7 (16·7)	120·5 (18·9)*	101·0 (20·8)*
RVET (ms)	192·8 (13·5)	215·0 (17·4)*	200·6 (16·0)
RPEP.RVET	0·51 (0·12)	0·34 (0·07)*	0·32 (0·03)*
AcT:RVET	0·37 (0·09)	0·56 (0·07)*	0·52 (0·05)*
LPEP (ms)	76·9 (13·1)	78·4 (11·0)	69·8 (7·5)
AcT (ms)	55·4 (9·7)	53·2 (7·6)	60·5 (14·3)
LVET (ms)	204·3 (21·5)	194·9 (16·6)	189·4 (14·4)
LPEP:LVET	0·36 (0·05)	0·40 (0·06)	0·37 (0·05)
AcT:LVET	0·27 (0·04)	0·27 (0·04)	0·30 (0·03)

RPEP, right pre-ejection period; RVET, right ventricular ejection time; AcT, acceleration time; LPEP, left pre-ejection period; LVET, left ventricular ejection time

*p < 0·01 compared with 0 day old neonates.

and averaged to obtain the final systolic time interval and AcT. PEP, AcT, and ET were determined in 12 recordings by one observer on two occasions. The intra-observer variability for PEP, AcT, and ET was 3%, 4%, and 2% respectively. The ductal patency was also evaluated by means of diastolic forward flow at the pulmonary end of the ductus.

Data were expressed as mean (SD) and were compared with those of other groups by Student's unpaired *t* test. A probability value <0·01 in the two tailed test was considered to be significant.

Results

FLOW VELOCITY PATTERN OF RIGHT AND LEFT VENTRICULAR OUTFLOW TRACT

The flow velocity pattern of the right ventricular outflow tract was initially triangular with a peak velocity in early systole; this changed to a dome-like contour with a peak velocity in mid-systole (fig 1a).

The mean right ventricular AcT increased from a mean of 68·7 ms in the 0 day old neonates to

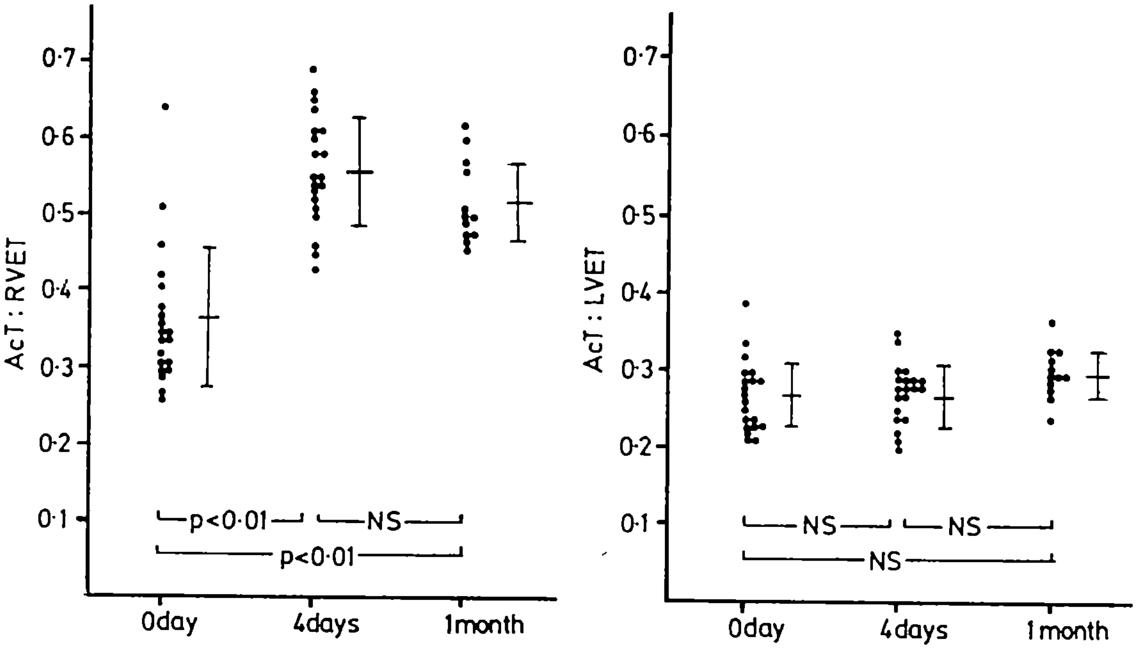

Fig 2 *AcT:RVET and AcT:LVET at three ages AcT, acceleration time; RVET, right ventricular ejection time; LVET, left ventricular ejection time. Means (1 SD) are shown.*

120·5 ms in the 4 day olds and to 101·1 ms in the 1 month olds (table).

The mean AcT:RVET ratio increased significantly with age from 0·37 in the 0 day olds to 0·56 in 4 day olds and to 0·52 in 1 month olds (fig 2). None of AcT:RVET ratios was <0·42 in the older groups. In all 10 infants who were examined on two occasions the AcT:RVET ratio was higher at the second examination (fig 3).

The flow velocity pattern of the left ventricular outflow tract was also triangular with a peak velocity in early systole, but this pattern did not change with increasing age (fig 1b). The mean left ventricular AcT varied from 53·2 to 60·5 ms (table) and the mean AcT:LVET ratio varied from 0·27 to 0·30 (fig 2).

RIGHT AND LEFT VENTRICULAR SYSTOLIC TIME INTERVALS

Right ventricular systolic time intervals changed significantly with age (table). The right ventricular pre-ejection period (RPEP) decreased from a mean of 93·8 ms in the 0 day olds to 72·1 ms in the 4 day olds and to 64·3 ms in the 1 month olds.

The right ventricular ejection time (RVET) increased from a mean of 192·8 ms in 0 day olds to 215·0 ms in 4 day olds and then decreased to 200·6 ms in the 1 month olds. The mean heart rate of 1 month olds was increased. The mean RPEP:RVET ratio declined from 0·51 in 0 day olds to 0·34 in 4 day olds and to 0·32 in the 1 month olds (fig 4). A second examination in 10 neonates showed a decreased RPEP:RVET ratio (fig 3).

Left ventricular systolic time intervals showed no significant variation with age (table). The mean left ventricular pre-ejection period (LPEP) varied from 69·8 to 78·4 ms and the mean left ventricular ejection time (LVET) varied from 189·4 to 204·3 ms. The mean LPEP:LVET ratio varied from 0·36 to 0·40 (fig 4).

PATENCY OF THE DUCTUS ARTERIOSUS

Left to right shunt flow through the ductus was detected with pulsed Doppler echocardiography in all 0 day old neonates, whereas none of the 4 day old or the 1 month old neonates had ductal flow.

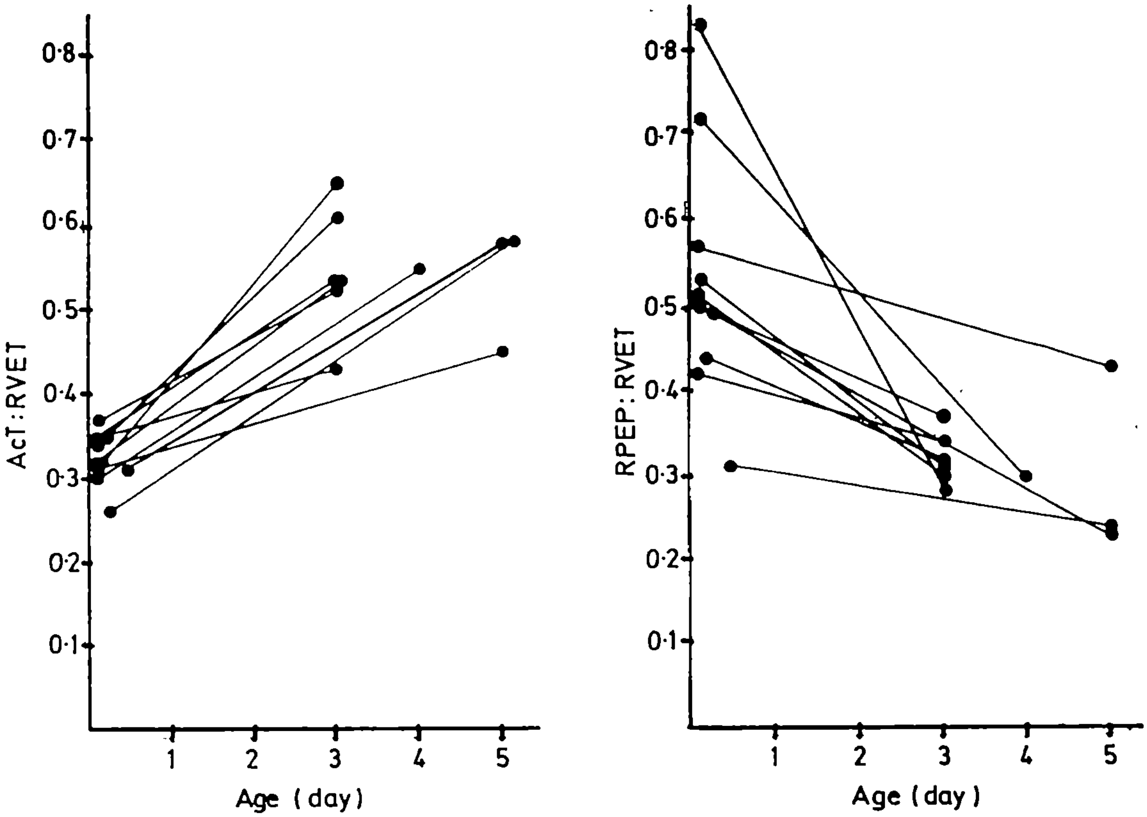

Fig 3 *Sequential AcT:RVET and RPEP:RVET ratio in 10 neonates. RPEP, right pre-ejection period; RVET, right ventricular ejection time; AcT, acceleration time.*

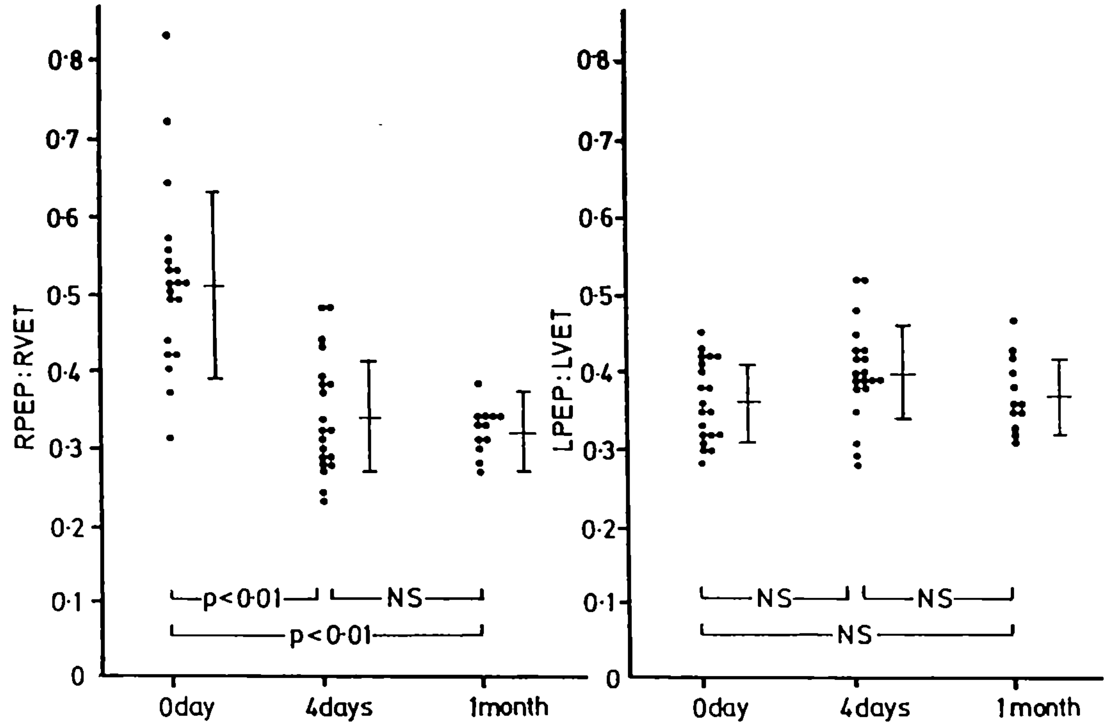

Fig 4 *RPEP:RVET ratio and LPEP:LVET ratio at three ages. RPEP, right pre-ejection period; RVET, right ventricular ejection time; LPEP, left pre-ejection period; LVET, left ventricular ejection time. Means (1 SD) are shown.*

Dicussion

M mode and cross sectional echocardiograms have been widely used to evaluate cardiac function,[8] to diagnose congenital heart diseases,[9] and to assess the pulmonary vascular bed.[10 11] These non-invasive techniques are especially useful in neonates. Detailed pulsed Doppler echocardiographic studies of the haemodynamic status of normal or diseased neonates, however, have not been performed before.

We found that the shape of the flow velocity envelope of the right ventricular outflow tract in healthy infants changed considerably in the early neonatal period from a triangular shape to a dome-like contour; this was confirmed by an increase in AcT:RVET ratio. We considered that an AcT:RVET ratio of <0.42 indicated the presence of pulmonary hypertension. This change may reflect a decrease of pulmonary artery pressure.[1] The change in the AcT:RVET ratio is regarded as an indicator of pulmonary vascular resistance and pulmonary artery pressure in laboratory animals[12] and patients with pulmonary hypertension.[4 5] Franklin *et al* reported the pattern of right ventricular ejection as a gradual increase in flow with a rounded peak in mid-systole and that of the left ventricular ejection as an abrupt increase in flow with a sharp peak in early systole. As pulmonary artery resistance increases the ejection pattern of the right ventricle approaches that of the left ventricle.[12] With pulsed Doppler echocardiography the flow velocity pattern of the right ventricular outflow tract in normal controls has a dome-like contour with a peak velocity in mid-systole, whereas in patients with pulmonary hypertension the envelope is triangular with a peak velocity in early systole.[4 5] Thus pulsed Doppler echocardiography may be used to detect raised pulmonary artery pressure.[4] The rapid acceleration of the flow in the pulmonary artery appears to be caused by the increased peak dP/dt of the pressure load of each ventricle,[13] and the early deceleration of the flow appears to be caused by the high total pulmonary vascular resistance and increased pulmonary vascular impedance.[14] Okamoto *et al* reported that the triangular envelope of the flow pattern is a specific feature of the pulmonary ejection in patients with pulmonary hypertension.[4] Kitabatake *et al* examined the flow velocity pattern in the right ventricular outflow tract in adults with pulmonary hypertension and found that AcT or AcT:RVET decreased as pulmonary artery pressure increased.[5]

Pulmonary artery pressure has been evaluated from the flow pattern obtained at the main pulmonary artery by pulsed Doppler echocardiography.[15] The flow in the main pulmonary artery in the early neonatal period is likely to be affected by the shunt flow through the ductus arteriosus. This is why we used the flow pattern of the right ventricular outflow tract to assess the pulmonary vascular bed.

Cardiac catheterisation in normal infants has shown that pulmonary artery pressure is high soon after birth and gradually falls in the first days of life.[1]

Variables other than these direct measurements have been used to assess the pulmonary vascular bed non-invasively. The systolic time interval, which appears to be influenced by factors such as afterload, myocardial contractility, ventricular electrical activation, preload, or heart rate,[16 17] is one of the non-invasive variables that has been used to evaluate cardiac function and the pulmonary vascular bed.[18] We used pulsed Doppler echocardiography to measure the systolic time intervals of the right and left ventricles. There was a clear decline of absolute RPEP and RPEP:RVET ratio in the early neonatal period. These findings are compatible with the previous reports in which M mode echocardiography was used.[10] Our method determines the onset and the end of the ejection more accurately. The pre-ejection period of each ventricle was, however, longer in our study. The time lag between sampling and frequency analysis was probably responsible for this.[6 7] Riggs *et al* obtained serial M mode echocardiograms from normal full term infants and measured right ventricular systolic time intervals from the pulmonary valve echo.[10] They showed that alterations in the RPEP:RVET ratio reflected the decreasing pulmonary artery pressure and pulmonary vascular resistance in the early neonatal period.

Another important aspect in our study is the assessment of the patency of the ductus arteriosus. In all the 0 day olds there was forward flow at the pulmonary end of the ductus during diastole indicating patency of the ductus. No forward flow was detected in older neonates. Pulsed Doppler examination in combination with cross sectional echocardiography is a non-invasive and highly sensitive method of evaluating the patency of the ductus arteriosus.[19 20] The ratio of LPEP:LVET was slightly but not significantly lower in the 0 day old neonates. This might be the result of increased preload and decreased afterload of the left ventricle caused by the left to right shunt through the ductus arteriosus. Pulmonary artery pressure did not fall abruptly after the establishment of respiration despite a considerable decrease in the pulmonary vascular resistance.[1] We did not measure the shunt through the ductus; however, an increase in pulmonary blood flow caused by the left to right shunt may have influenced pulmonary artery pressure and pulmonary vascular resistance in the neonates who were <12 hours old.

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References

1 Adams FH. Fetal and neonatal circulations. In: Adams FH, Emmanouilides GC, eds. *Heart disease in infants, children and adolescents*. Baltimore: Williams and Wilkins, 1983:11–7.

2 Pearlman AS, Lighty GW Jr. Clinical applications of two-dimensional/Doppler echocardiography. *Cardiovasc Clin* 1983;**13**:201–22.

3 Stevenson JG. Doppler evaluation of common shunt lesions in congenital heart disease. In: Nanda NC, ed. *Doppler echocardiography*. New York and Tokyo: Igakushoin, 1985:393–415.

4 Okamoto M, Miyatake K, Kinoshita N, Sakakibara H, Nimura Y. Analysis of blood flow in pulmonary hypertension with the pulsed Doppler flowmeter combined with cross sectional echocardiography. *Br Heart J* 1984;**51**:407–15.

5 Kitabatake A, Inoue M, Asao M, Masuyama T, Tanouchi J, Morita T. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983;**68**:302–9.

6 Matsuo H, Morita H. Current status of pulsed Doppler method. *J Cardiogr* 1984;**14**(suppl II):27–39. (In Japanese.)

7 Sanada J, Nakamura K, Minami Y, *et al*. Pulsed Doppler echocardiographic assessment of mitral regurgitation. *Jpn J Med Ultrasonics* 1983;**10**:5–13. (In Japanese.)

8 Gutgesell HP, Pinsky WW, Duff DF, Adams J, McNamara DG. Left and right ventricular systolic time intervals in the newborn: usefulness and limitation in distinguishing respiratory disease from transposition of the great arteries. *Br Heart J* 1979;**42**:27–34.

9 Macartney FJ. Cross sectional echocardiographic diagnosis of congenital heart disease. *Br Heart J* 1983;**50**:501–5.

10 Riggs T, Hirschfeld S, Bormuth C, Fanaroff A, Liebman J. Neonatal circulatory changes: an echocardiographic study. *Pediatrics* 1977;**59**:338–44.

11 Riggs T, Hirschfeld S, Fanaroff A, *et al*. Persistence of fetal circulation syndrome: an echocardiographic study. *J Pediatr* 1977;**91**:626–31.

12 Franklin DL, Van Citters RL, Rushmer RF. Balance between right and left ventricular output. *Circ Res* 1962;**10**:17–26.

13 Gleason WL, Braunwald E. Studies on the first derivative of the ventricular pressure pulse in man. *J Clin Invest* 1962;**41**:80–91.

14 Reuben SR. Compliance of the human pulmonary arterial system in disease. *Circ Res* 1971;**29**:40–50.

15 Kosturakis D, Goldberg SJ, Allen HD, Loeber C. Doppler echocardiographic prediction of pulmonary arterial hypertension in congenital heart disease. *Am J Cardiol* 1984;**53**:1110–5.

16 Weisser AM, Lewis RP, Leighton RF. The systolic time intervals as a measure of left ventricular performance in man. In: Yu PN, Goodwin JF, eds. *Progress in cardiology*. Philadelphia: Lea and Febiger, 1972:155–83.

17 Leighton RF, Weissler AM, Weinstein PB, Wooley CF. Right and left ventricular systolic time intervals—effect of heart rate, respiration and atrial pacing. *Am J Cardiol* 1971;**27**:66–72.

18 Hirschfeld S, Meyer R, Schwartz DC, Korfhagen J, Kaplan S. The echocardiographic assessment of pulmonary artery pressure and pulmonary vascular resistance. *Circulation* 1975;**52**:642–50.

19 Huhta J, Cohen M, Gutgesell HP. Patency of the ductus arteriosus in normal neonates: two-dimensional echocardiography versus Doppler assessment. *J Am Coll Cardiol* 1984;**4**:561–4.

20 Gentile R, Stevenson JG, Dooley T, Franklin D, Kawabori I, Pearlman A. Pulsed Doppler echocardiographic determination of time of ductal closure in normal newborn infants. *J Pediatr* 1981;**98**:443–8.

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Aortic valve damage caused by operative balloon dilatation of critical aortic valve stenosis

RACHEL R PHILLIPS, LEON M GERLIS, NEIL WILSON, DUNCAN R WALKER

From the Regional Cardiothoracic Unit, Killingbeck Hospital, Leeds

SUMMARY Operative balloon dilatation of the aortic valve was performed in seven neonates with critical stenosis of the aortic valve. The procedure was followed by the development of severe aortic regurgitation in four patients. Necropsy was performed in three and revealed partial detachment of the right coronary cusp of the aortic valve. Damage to the valve leaflet caused by balloon dilatation was probably the result of using a balloon with a diameter that was too large in relation to the aortic valve ring diameter and of shearing forces created in the aortic wall by the contracting ventricle. The diameter of the inflated balloon should not be larger than the diameter of the aortic valve ring.

Percutaneous balloon dilatation of the pulmonary[1] or aortic valve[2 3] has been used to relieve critical valvar stenosis in children and adults.[4] Experimental and necropsy findings after this procedure have shown linear tears of the valve or transverse tears in the aortic wall.[5] We report four cases of operative balloon dilatation of the aortic valve that damaged the valve leaflets.

Patients and methods

Seven infants underwent operative balloon dilatation of critical aortic stenosis presenting in the neonatal period.

CASE 1

A female baby presented in cardiac failure at the age of four days. Echocardiography and angiocardiography revealed a ventricular septal defect, severe aortic stenosis, ductus arteriosus, and preductal coarctation. She underwent surgical repair of the coarctation with a Goretex gusset and ligation of the ductus arteriosus on the eighteenth day of life. Postoperatively episodes of acute left ventricular failure that were unresponsive to medical treatment developed and she required further mechanical ventilation. These episodes were caused by massive left to right shunting through the ventricular septal defect, which was worsened by the critical obstruction of the left ventricular outflow tract. The echocardiographic estimate of the diameter of the valve ring was 6 mm. On the forty-seventh day the ventricular septal defect was closed surgically and at the same time balloon dilatation of the aortic valve was performed through an apical left ventricular stab incision with an 8 mm diameter balloon catheter. There was some improvement immediately after the operation but she died the next day.

CASE 2

A female baby presented with a systolic murmur and cardiac failure on the second day of life. Echocardiography revealed critical aortic stenosis with an estimated valve ring diameter of 5–6 mm. She developed clinical signs of necrotising enterocolitis on the second day, which responded to conservative treatment. She underwent operative balloon dilatation of the aortic valve on the sixteenth day with a 12 mm diameter balloon catheter but immediately bradycardia with low cardiac output developed, and she died in the operating theatre.

CASE 3

This 36 hour old male baby presented in cardiac failure. Echocardiography revealed critical aortic stenosis with a valve ring diameter of 6 mm. He was severely acidotic. He underwent operative balloon dilatation of the aortic valve with a 12 mm diameter balloon catheter on the second day of life. The procedure was followed by slow postoperative

Requests for reprints to Dr Neil Wilson, Department of Paediatric Cardiology, Killingbeck Hospital, York Road, Leeds LS14 6UQ.

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improvement but on the seventh postoperative day he collapsed because of septicaemia and died of a cerebral haemorrhage 24 hours later.

CASE 4

A female baby presented in cardiac failure 24 hours after birth. Echocardiography showed critical aortic stenosis with an 8 mm diameter valve ring. On the second day of life she underwent operative balloon dilatation of the aortic valve with an 8 mm diameter balloon catheter. Postoperative Doppler echocardiography showed satisfactory relief of the stenosis with a maximum gradient of 30 mm Hg but also showed the development of severe aortic regurgitation. She required further medical treatment and mechanical ventilation for left ventricular failure secondary to the aortic regurgitation, and aortic valve replacement was planned in view of her intractable cardiac failure. On the twenty-fourth day the aortic root was replaced by her own pulmonary valve; the coronary arteries were reimplanted with a homograft replacement to the right ventricular outflow tract. Immediately after this procedure bradycardia developed and she died in the operating theatre. Necropsy was not performed.

NECROPSY FINDINGS

In the first three cases postmortem examination of the heart showed dysplastic bicuspid aortic valves. In patient 1 the original orifice was narrowed to 2·5 mm in diameter, with a valve ring diameter of 4 mm. Further inspection of the valve disclosed a 3 mm tear that detached the base of the right side of the right coronary cusp from its attachment to the ring, producing aortic incompetence (fig (a)).

In patient 2 there was almost complete detachment (4 mm in length) of the right coronary cusp from its marginal attachment. There was also a linear longitudinal tear 5 mm long through the subvalvar endocardium and the intima of the base of the aortic wall. This appeared to have been a consequence of the forcible detachment of the cusp (fig (b)).

In patient 3 the diameter of the aortic valve ring was 4 mm and the valve consisted of a thickened nodular dysplastic structure that had been split by a T shaped tear and partly detached from the margin over a 3 mm length on the posteromedial aspect (fig (c)).

The use of balloon dilatation in critical aortic stenosis was successful in three of our cases. Our four unsuccessful cases clearly represent the most severe end of the spectrum of critical aortic stenosis. Of the successful cases, patient A, a boy, had previously undergone open surgical aortic valvotomy for critical aortic stenosis (valve ring diameter of 3 mm) when he was 20 days old. Balloon dilatation of the aortic valve was performed for restenosis when he was eight months old. The echocardiographic estimate of the diameter of his aortic valve ring was 6–7 mm (gradient 80 mm Hg on Doppler echocardiography). A balloon catheter with an inflated

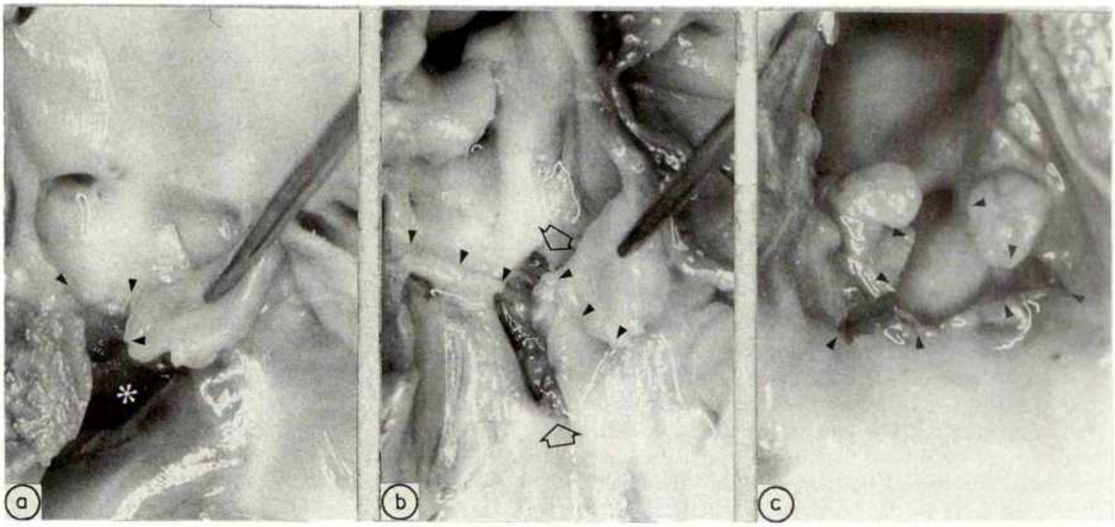

Figure *The opened aortic valves and left ventricular outflow regions at necropsy in three patients. The small arrows indicate the extent of the cusp tears. (a) Female infant aged 47 days. Asterisk indicates ventricular septal defect. (b) Female infant aged 16 days. The open arrows indicate the additional longitudinal tear. (c) Male infant aged 9 days. The T shaped tear has divided the cusp and has also caused peripheral detachment.*

diameter of 10 mm was used. Despite mild aortic regurgitation, he remains well clinically five months after the procedure.

Patient B, a boy, had repair of aortic coarctation at 23 days of age. Doppler echocardiography at the time revealed mild aortic stenosis (gradient 40 mm Hg with good left ventricular function). Cardiac failure due to severe aortic stenosis (gradient 90 mm Hg, valve ring diameter 10 mm) with a poorly contracting left ventricle developed when he was eight weeks old. Balloon dilatation of the aortic valve was performed with a 10 mm diameter balloon, and postoperatively Doppler echocardiography showed a maximum gradient of 30 mm Hg with mild regurgitation and improved left ventricular function. He remains well at six months of age.

Patient C presented in cardiac failure 14 days after birth. Doppler echocardiography showed critical aortic stenosis with a gradient of 60 mm Hg and a valve ring diameter of 8 mm. Operative balloon dilatation was performed on the fifteenth day with a 6 mm diameter balloon and her postoperative recovery was uncomplicated. Repeat echocardiography showed a Doppler gradient of 40 mm Hg with no aortic regurgitation and she remains well at four months.

Discussion

Nearly all infants with critical aortic stenosis die soon after birth. Palliative procedures, including open aortic valvotomy or percutaneous balloon dilatation, are associated with substantial morbidity and mortality. In our hospital we elected to use balloon dilatation rather than the conventional Hegar dilators because of the potential advantages of a narrower initial balloon diameter and a more controllable dilatation technique. In all cases the balloon was 3 cm long but because it became fusiform when inflated across the valve the usable length was only 2 cm. We did not find that the balloon protruded through the valve when we used a left ventricular stab incision but a shorter balloon would be more suitable and as effective.

Although there was an initial improvement after the procedure in our seven patients, injury to the aortic valve cusps in four (particularly the right coronary cusp) was sufficient to cause uncontrollable aortic regurgitation. Damage to the aortic wall has already been linked with the ratio of the diameter of the inflated angioplasty balloon to the aortic lumen.[5] Transverse tears in the aortic wall were produced when a balloon with an inflated diameter similar to or larger than the diameter of the aorta was used. The aortic wall is elastic and is able to stand moderate stretching without damage, whereas the valve ring (in a dysplastic valve especially) is rigid and is more likely to tear at a degree of dilatation that does not damage the aortic wall. This apparent tolerance of the arterial wall to stretching has been confirmed in animal experiments in which oversized balloons were inflated across the pulmonary valve[6]; major damage to the heart occurred in the outflow tract of the right ventricle. This study, however, was of normal pulmonary valves and thus the additional effect of the rigidity of a dysplastic valve could not be evaluated. Damage of the sort described above[5 6] appeared to have occurred in our cases that came to necropsy, and in patient 2 the tear extended upwards into the aortic wall and downwards into the ventricle. The ventricular extension was very close to the bundle of His and damage to this structure may have been associated with the terminal bradycardia. The balloon size in these three cases was 8 mm, 12 mm, and 12 mm; in all three the diameter of the valve ring was 4 mm at necropsy. In patient 4 the balloon diameter was 8 mm and the valve ring diameter was 8 mm. The shearing effect of the inflated balloon in a contracting ventricle is a further probable cause of damage.

It seems that to avoid important damage both to the aortic wall and to the valve leaflets, while still producing effective dilatation of a critically stenosed aortic valve, a balloon with an inflated diameter of somewhat less than the diameter of the aortic valve ring should be used. Furthermore, the duration of balloon dilatation should be kept to a minimum to lessen the shearing force produced by the contracting ventricle.

We intend further evaluation of this technique for the relief of critical aortic stenosis, but in the light of our findings we will use a balloon with a diameter that is 70%–80% of the echocardiographic estimate of the diameter of the valve ring.

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References

1 Rocchini AP, Kveselis DA, Crowley D, Dick M, Rosenthal A. Percutaneous balloon valvuloplasty for treatment of congenital pulmonary valvular stenosis in children. *J Am Coll Cardiol* 1984;**3**:1005–12.

2 Lababidi Z, Wu JR, Walls J. Percutaneous balloon aortic valvuloplasty. *Am J Cardiol* 1984;**53**:194–7.

3 Sanchez GR, Mehta AV, Ewing LL, Brickley SE, Anderson TM, Black IFS. Successful percutaneous balloon valvuloplasty of the aortic valve in an infant. *Pediatr Cardiol* 1985;**6**:103–6.

4 Gibbs JL, Stanley CP, Dickinson DF. Pulmonary balloon valvuloplasty in late adult life. *Int J Cardiol* 1986;**11**:237–9.

5 Waller BF, Girod DA, Dillon JC. Transverse aortic wall tears in infants with balloon angioplasty for aortic valve stenosis. *J Am Coll Cardiol* 1984;**4**:1235–41.

6 Ring JC, Kulik TJ, Burke BA, Lock JE. Morphologic changes induced by dilatation of the pulmonary valve annulus with overlarge balloons in newborn lambs. *Am J Cardiol* 1984;**55**:210–4.

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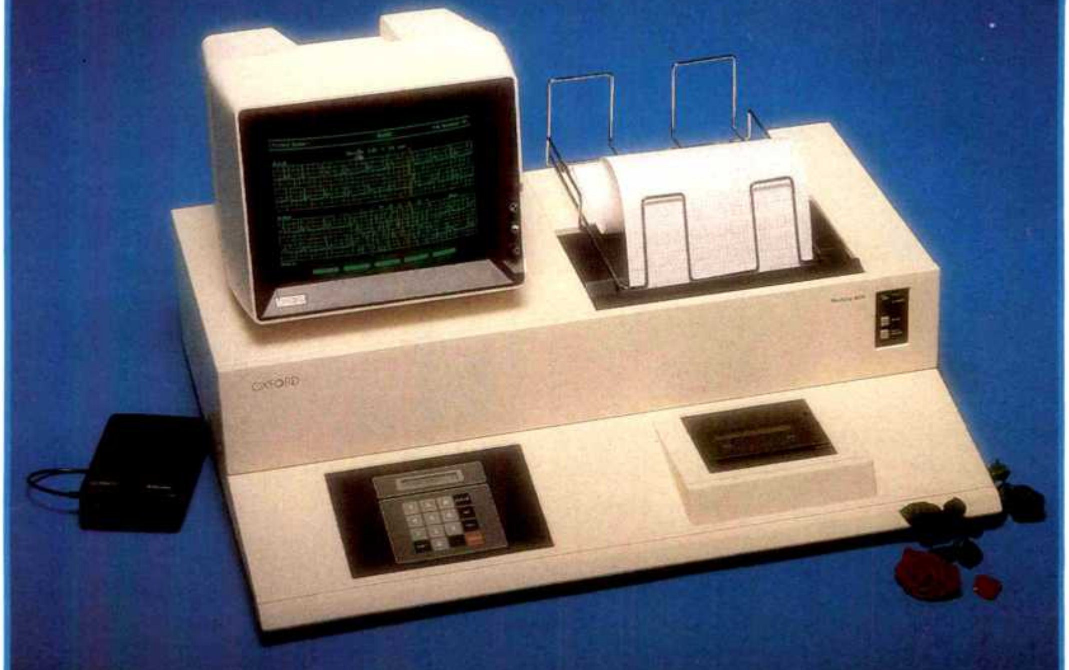

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The response of paediatric arrhythmias to intravenous and oral flecainide

CHRISTOPHER WREN, RONALD W F CAMPBELL

From the Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne

SUMMARY Flecainide acetate was administered intravenously and orally to 12 consecutive children, aged 1–15 years, presenting with arrhythmias that were life threatening or resistant to conventional medical treatment. Three children had arrhythmias related to Wolff-Parkinson-White syndrome, four had concealed accessory pathways, two had His bundle tachycardia, and three had ventricular tachycardia. Of seven patients who were given flecainide intravenously, four returned to sinus rhythm and in a fifth successful rate control of His bundle tachycardia was achieved. All 12 patients were given the drug orally: in nine it was successful in preventing recurrence of arrhythmia, in one satisfactory rate control was achieved, and in two it was withdrawn because it produced more frequent attacks of tachycardia. No other adverse effects occurred.

The efficacy and low toxicity of treatment in this study suggests that flecainide acetate may have an important role in the management of selected paediatric arrhythmias.

Symptomatic and life threatening arrhythmias are fortunately relatively uncommon in paediatric practice. When they do occur their treatment is particularly demanding. Efficacy is obviously important but in infants and children drug toxicity is of special relevance, particularly when long term dosing may be necessary.

When arrhythmias in adults prove refractory to conventional management strategies, new drugs and investigational compounds are often tried. Caution in the institution of such treatment in children is justifiable as treatment may be necessary for many years, long term effects are unknown, and pharmacokinetic responses in children cannot be predicted from experience in adults.

Flecainide acetate, an antiarrhythmic drug with Vaughan Williams class IC actions, has rapidly become established in the management of a wide variety of arrhythmias in adults.[1–3] With the exception of arrhythmogenesis, it has a relatively low toxicity, has stable and reliable kinetics, and its half life of 8–12 hours facilitates dosing twice or three times a day. Experience with the use of flecainide in children is limited[4 5] but these properties suggest a potentially important role in paediatric practice.

This report describes our experience of using intravenous and oral flecainide in 12 children with life threatening arrhythmias or arrhythmias that were difficult to manage with conventional agents.

Patients and methods

PATIENTS

All 12 children (mean aged 8, range 1–15) presenting between May 1983 and October 1985 with arrhythmias that were potentially dangerous or had failed to respond to at least one conventional antiarrhythmic agent were treated with flecainide (table 1). Only four patients had associated structural heart disease. The mechanism of the arrhythmia was confirmed at electrophysiological study in nine patients and was apparent from the surface electrocardiogram in the other three. Ten patients had received previous drug treatment (six intravenously and eight orally), which had been unsuccessful. Before administering flecainide, five half lives of any previous antiarrhythmic therapy were allowed to elapse to clear that drug from the circulation. In the two patients who had taken amiodarone this was not possible: the drug withdrawal period was three months in patient 8 and three weeks in patient 9.

Requests for reprints to Professor Ronald W F Campbell, Department of Academic Cardiology, Freeman Hospital, Newcastle upon Tyne NE7 7DN.

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Table 1 *Details of patients and previous drug treatment*

Case No	*Age (years)*	*Sex*	*Weight (kg)*	*Diagnosis*	*Rate (beats/min)*	*Other diagnosis*	*Failed iv drugs*	*Failed oral drugs*	*Follow up (months)*
1	9	M	36	CAP*	200	—	—	Dg Pt Pr V Q	39
2	11	F	27	CAP*	195	1°ASD	V	—	33
3	13	F	66	CAP*	190	—	—	Dg Pr	27
4	13	M	40	CAP*	180	—	—	Dg	21
5	13	F	47	WPW*	172	CTGA	Dg	—	31
6	13	F	43	WPW*	200	Ebstein's anomaly	—	V	17
7	7	M	26	WPW*	230	—	Dg V	Dg Q V Ds Fc	12
8	15	M	49	HBT*	160	CTGA	Pr Pc Dg V	Dg Q A	26
9	2	M	13	HBT*	210	—	Dg V	Dg Pr Q A	23
10	1	F	12	VT	220	—	Dg V Ds	Dg Ds Pr	22
11	2	F	11	VT	360	—	—	—	16
12	1	M	9	VT	290	—	—	—	10

iv, intravenous; A, amiodarone, Dg, digoxin; Ds, disopyramide, Fc, flecainide; Pc, procainamide; Pr, propranolol; Pt, practolol; Q, quinidine; V, verapamil; 1°ASD, ostium primum atrial septal defect; CTGA, corrected transposition of the great arteries; CAP, concealed accessory pathway; WPW, Wolff-Parkinson-White syndrome, HBT, His bundle tachycardia; VT, ventricular tachycardia.
*Confirmed at electrophysiology study

Table 2 *Response to intravenous and oral flecainide*

Intravenous			*Oral*				
Case No	*Dose (mg)*	*Response*	*Daily dose (mg)*	*(mg/kg)*	*Response*	*Plasma concentration (μg/l)*	*(mmol/l)*
1	20	→SR	100	3·7	NR	535	1·13
2	—	—	200	3·0	NR		
3	25	→SR	100	2·7	NR		
4	—	—	200	5·0	F		
5	90	Slowed	150	3·5	NR	417	0·88
6	20	→SR	300	6·4	F		
7	30	→SR	250	9·6	NR	463	0·98
8	25	Slowed 210→130	150	11·5	RC	343	0·72
9	100	Slowed 150→120	200	4·1	NR	396	0·84
10	—	—	75	6·3	NR	410	0·86
11	—	—	75	6·8	NR		
12	—	—	200	22·2	NR	492	1·04

→SR, reverted to sinus rhythm, NR, no recurrence; RC, rate controlled; F, failed, —, not given

FLECAINIDE ADMINISTRATION

Flecainide was given intravenously to seven children during tachycardia that either had occurred spontaneously or was induced at electrophysiological study (table 2). The maximum dose was 2 mg/kg. Thereafter all seven received oral treatment. Oral treatment in all 12 children was started in doses of 3–6 mg/kg/day and increases were guided by the patient's response and, in some cases, by plasma concentrations. The maximum oral dose was 22 mg/kg/day. For the two youngest children, flecainide was made into a syrup or suspension. The other children were given standard tablets; some took them crushed in yoghurt or other palatable food. Twice daily dosing was used where possible and three times daily dosing was advised in four patients taking small doses. All patients were monitored in hospital during the initiation of treatment. They were allowed home when they were seen to tolerate the drug or, in those with His bundle or ventricular tachycardia, when 24 hour electrocardiographic monitoring confirmed suppression of the arrhythmia.

TREATMENT ASSESSMENT

Intravenous treatment was judged to be successful if the arrhythmia was terminated or, in the case of incessant ectopic arrhythmias, if a clinically beneficial reduction in rate was obtained. Any other response was regarded as a failure. Long term treatment was judged to be a success if there was no recurrence of arrhythmia, or if there was no more than an occasional minor episode of tachycardia, or if long term rate control was achieved in incessant arrhythmias. Any other response was regarded as a failure. Trough concentrations of plasma flecainide were measured in seven patients. Plasma concentrations were used to adjust dosing only if the arrhythmia persisted. Follow up assessment was by history of recurrence of symptoms, 12 lead electrocardiogram, and 24 hour ambulatory monitoring.

Results

All patients satisfying the inclusion criteria had one of the following arrhythmias: atrioventricular reentry by an accessory pathway, His bundle tachycardia, or ventricular tachycardia. We expected that the response to flecainide would vary depending on the mechanism of the arrhythmia, and the analysis of the clinical results was based on this premise.

CONCEALED ACCESSORY PATHWAY (FOUR PATIENTS)

In all patients the arrhythmias were orthodromic reentry tachycardias with rates of 180–200 impulses/minute. In both patients given intravenous flecainide sinus rhythm was restored promptly and in one this was due to a block in the accessory pathway. Three patients have had no recurrence of arrhythmia since the start of oral treatment. The fourth (patient 4) experienced more frequent episodes of tachycardias on oral flecainide and these could not be controlled by increasing the dose. He is now symptom free on treatment with disopyramide.

WOLFF-PARKINSON-WHITE SYNDROME (THREE PATIENTS)

Intravenous flecainide terminated an orthodromic tachycardia in two patients (in the retrograde limb in both instances) and on return to sinus rhythm there was no evidence of preexcitation. In one of these (patient 5) oral flecainide caused more frequent episodes of tachycardia although there was a persisting anterograde block in the pathway. Symptomatic control could not be achieved and flecainide was discontinued and replaced by disopyramide.

Patient 6 had two accessory pathways. When flecainide was given intravenously during orthodromic tachycardia the cycle length increased and the atrial activation pattern changed, suggesting retrograde block in one of the pathways, although the reentry tachycardia persisted and had to be terminated by programmed stimulation. Despite this response there has been no recurrence of symptoms since the start of oral flecainide.

Patient 7 had already received oral flecainide in a dose of 4 mg/kg/day at his referring hospital and his episodes of tachycardia had become more frequent. Because intravenous flecainide given during electrophysiological study produced bidirectional block in the pathway, he was given a higher oral dose (10 mg/kg/day) and he is now free from symptoms.

HIS BUNDLE TACHYCARDIA (TWO PATIENTS)

Patient 8 had had episodes of ectopic His bundle tachycardia since infancy. Intravenous flecainide slowed the arrhythmia but failed to terminate it. Because all conventional antiarrhythmic drugs had been unsuccessful, oral flecainide was started and there has been no recurrence during 26 months follow up.

In patient 9 the rate of an incessant His bundle tachycardia was reduced from 210 to 130 impulses/minute by intravenous flecainide and satisfactory rate control has been maintained on oral treatment (with a resting heart rate of about 90 beats/minute and a maximum rate of 140 beats/minute on ambulatory monitoring).

VENTRICULAR TACHYCARDIA (THREE PATIENTS)

Two children had paroxysmal uniform ventricular tachycardia (patient 10, rate 220; patient 11, rate 290 beats/minute) and the third (patient 12) had frequent self-terminating episodes of multiform ventricular tachycardia with rates of 320–400 beats/minute lasting for up to several minutes at a time. The clinical history suggested the presence of a tachycardia for nine months, two weeks, and three weeks respectively. Despite the rate of the tachycardias, all three children were haemodynamically stable and oral treatment was started. Flecainide has successfully controlled the arrhythmias in all three, with no recurrences. In patient 12 a progressive increase in dose was monitored with plasma concentrations.

Table 3 *Results for each arrhythmia*

		Intravenous			*Oral*		
Diagnosis	*No*	*No*	*Success*	*Failure*	*No*	*Success*	*Failure*
CAP	4	2	2	—	4	3	1
WPW	3	3	2	1	3	2	1
HBT	2	2	1	1	2	2	—
VT	3	—	—	—	3	3	—
Total	12	7	5	2	12	10	2

CAP, concealed accessory pathway, WPW, Wolff-Parkinson-White syndrome; HBT, His bundle tachycardia; VT, ventricular tachycardia

Daily doses of 60 mg, 100 mg, 150 mg, and 200 mg produced plasma concentrations of 155, 114, 450, and 492 μg/l (0·33, 0·24, 0·95, and 1·04 mmol/l) respectively and suppression of ventricular tachycardia was achieved only on the highest dose.

OVERALL RESULTS (TABLE 3)

Seven patients were given intravenous flecainide during tachycardia. In four sinus rhythm was restored by 0·4–1·0 mg/kg of the drug. In the other three the arrhythmia persisted although the rate was reduced; but in only one was this a satisfactory response.

All 12 patients received oral flecainide and in 10 treatment has been successful. In two patients with accessory pathways oral flecainide was withdrawn because it caused more frequent symptoms; although in both cases intravenous flecainide had produced complete block in the pathway.

All patients who received intravenous flecainide were subsequently given the drug orally. Successful intravenous treatment predicted continuing clinical benefit on oral treatment in four of five patients. In two patients (6 and 8), despite a poor response when the drug was given intravenously, oral flecainide has proved successful in preventing recurrence of the arrhythmia.

UNWANTED EFFECTS

With the exception of the exacerbation of arrhythmia in the two patients described above, no unwanted effects were observed or reported during intravenous treatment or during 276 patient-months of follow up.

Plasma concentrations

Results were obtained in seven patients (table 2) and on doses of 2·7–22·2 mg/kg/day they ranged from 343 to 535 μg/l (0·72–1·13 mmol/l) which is within the lower end of the therapeutic range in adults. No abnormalities of haematological and biochemical indices were noted.

Discussion

Controlled randomised clinical trials of antiarrhythmic drugs are scientifically important, but such study designs are not applicable to all clinical situations. Rare arrhythmias (that preclude the enrolment of adequate numbers of patients in a study), serious life threatening arrhythmias (raising ethical objections), medically refractory arrhythmias (introducing selection bias because of previously tested agents), and arrhythmias in children (demanding exceptional short and long term safety) are perhaps the most clinically important arrhythmias but are those least suitable for controlled antiarrhythmic drug studies. In this open study, flecainide acetate was given to paediatric patients who had manifest serious and/or medically refractory arrhythmias. Flecainide was chosen because its electrophysiological actions have been well examined[6] and because it is important in the management of arrhythmias in adults, including ventricular tachycardia[2] and the arrhythmias associated with the preexcitation syndrome.[3]

In 10 of 12 patients an excellent therapeutic response was obtained either by complete suppression of the arrhythmia or by control of ventricular rate. In eight of these 10 patients other antiarrhythmic drugs had been ineffective or poorly tolerated, including amiodarone in two children.

Arrhythmogenesis occurred in two patients with tachycardias caused by accessory pathways. Occasional arrhythmogenesis has been reported before[4] and might be predicted by the drug's electrophysiological effects. Slowed conduction may increase the excitable gap of reentrant arrhythmias, enhancing tachycardia although slowing its rate.

The pharmacokinetics of flecainide in children are not established. Plasma flecainide concentrations were not investigated systematically in this study but results in seven patients were at the lower end of the adult therapeutic range.[7] Adult patients are rarely given more than 4–5 mg/kg/day, whereas half of our patients required more than 5 mg/kg/day. Even allowing for differences in body surface area these doses are higher than those used in adults; this feature accords with paediatric use of other antiarrhythmic drugs.

The place of flecainide in the treatment of paediatric arrhythmias will be determined by further experience and long term follow up. Nevertheless, this demonstration of the drug's efficacy, safety, and relative freedom from unwanted effects suggests that it will be important in the management of selected paediatric arrhythmias and may prove an attractive alternative to more toxic antiarrhythmic drugs.[8 9]

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References

1 Hellestrand KJ, Nathan AW, Bexton RS, Spurrel RAJ, Camm AJ. Cardiac electrophysiologic effects of flecainide acetate for paroxysmal reentrant junctional tachycardias. *Am J Cardiol* 1983,51:770–6.
2 Anderson JL, Stewart JR, Perry BA, *et al.* Oral flecainide acetate for the treatment of ventricular arrhythmias. *N Engl J Med* 1981,305:473–7.

3 Neuss H. Long term use of flecainide in patients with supraventricular tachycardia. *Drugs* 1985;29(suppl 4):21–5.

4 Pfefferkorn J, Hilgenberg F. Erste Erfahrungen mit Flecainid im Kindesalter. *Drug Evaluation and Development* 1984;8:167–73.

5 Ward DE, Jones S, Shinebourne EA. Use of flecainide acetate for refractory junctional tachycardia in children with the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1986;57:787–90.

6 Estes NAM, Garan H, Ruskin JN. Electrophysiologic properties of flecainide acetate *Am J Cardiol* 1984;53:26B–9B.

7 Conard GJ, Ober RE. Metabolism of flecainide. *Am J Cardiol* 1984;53:41B–51B.

8 Garson A Jr, Gillette PC, McVey P, *et al.* Amiodarone treatment of critical arrhythmias in children and young adults. *J Am Coll Cardiol* 1984;4:749–55.

9 Bucknall CA, Keeton BR, Curry PVL, Tynan MJ, Sutherland GR, Holt DW. Intravenous and oral amiodarone for arrhythmias in children. *Br Heart J* 1986;56:278–84.

Br Heart J 1987;57:176–80

Cardiac damage in polymyositis associated with antibodies to tissue ribonucleoproteins

WILHELMINA M H BEHAN,* PETER O BEHAN,† JAN GAIRNS

*From the University Departments of *Pathology and †Neurology, Glasgow University, Glasgow*

SUMMARY Cardiac damage, consisting of mild diffuse myocarditis or severe inflammation and fibrosis of the conduction system or both, occurs in more than 70% of patients with idiopathic polymyositis. The lesions are strikingly similar to those detected in the infants of mothers with connective tissue diseases. In these infants the damage is associated with the transplacental passage of a maternal antibody to tissue ribonucleoproteins (anti-Ro). The same antibody was identified in 60% of 55 patients with polymyositis and in 69% (23/33) of those with associated cardiac damage including four with complete heart block. Forty five per cent of those patients who were anti-Ro seropositive had no clinical or electrocardiographic evidence of cardiac lesions. They were in the acute phase of illness, however, and no other more detailed heart investigations had been done.

It is postulated that cardiac damage in polymyositis is caused by the antibody and that its presence may serve as a marker for heart involvement.

Polymyositis is an inflammatory myopathy of unknown cause in which both hormonal and cellular abnormalities occur that may be related to a defect in immunoregulation.[1 2] Skeletal muscle bears the brunt of the disease but the skin (dermatomyositis), heart, lungs, eyes, and kidneys may also be affected.[2] Cardiac lesions are of particular importance both because of their frequency, which has only recently been fully documented, and because they are one of the leading causes of death in this disease.[3-5] Numerous published reports (reviewed by Askari and Huettner[3]) show that approximately 70% of cases of polymyositis have evidence of cardiac damage with the conduction system showing the severest lesions in one third of those affected. Complete heart block can occur and may cause sudden unexpected death.[5] In some cases, however, the lesions are confined entirely to the right or left bundle branch. The lesions found in the cardiac conduction system resemble those of the neonatal lupus syndrome,[6 7] in which transplacental passage of a maternal autoantibody to tissue ribonucleoproteins (anti-Ro) seems to cause the damage.[8] We have examined serum samples from a group of 55 well defined cases of polymyositis for anti-Ro.

Patients and methods

We examined serum samples collected from 55 patients with polymyositis over the past 10 years at Glasgow hospitals. In each case the diagnosis was based on clinical history, laboratory tests, electromyography, and muscle biopsy examination, according to stated criteria.[9] There were 17 male patients (aged 12–65 years, mean 38) and 38 women (aged 21–72 years, mean 46). They were classified into subgroups[9] as follows: subgroup I, pure polymyositis (13 cases); subgroup II, pure dermatomyositis (23 cases); subgroup III, polymyositis or dermatomyositis associated with neoplasia (two cases); subgroup IV, juvenile polymyositis or dermatomyositis (six cases); and subgroup V, polymyositis or dermatomyositis associated with other connective tissue diseases (11 cases). In the last group there were four cases of the mixed connective tissue disease syndrome, three with rheumatoid arthritis, and one with severe Raynaud's phenomenon.

Sixteen patients were examined in the acute phase of the disorder, from six weeks to three months after onset. In six of them a serum sample was obtained

Requests for reprints to Dr Wilhelmina M H Behan, Department of Pathology, Western Infirmary, Dumbarton Road, Glasgow G11 6NT.

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before treatment and in the other 10 it was collected after steroids had been given. The remaining 39 cases had had chronic active polymyositis for four months to 15 years. Thirty six were taking prednisolone (5–10 mg/day) and two of these were also on azothioprine (100 mg/day). Three patients were taking no drugs.

CARDIAC COMPLICATIONS

All patients had had electrocardiograms but most had no other cardiac investigations (table 1).

The symptoms varied in degree from breathlessness on exertion to severe biventricular failure and included angina, dyspnoea, and palpitation; five patients had Adams-Stokes attacks. The most common electrocardiographic abnormalities were ST-T changes, right and left axis deviation, and abnormalities of the left atrial complex; but 13 patients had obvious evidence of conduction disorders—that is, five had complete heart block necessitating insertion of a pacemaker, four had right or left bundle branch block, and four had first degree heart block. Three of the patients with complete heart block died and in the two who came to necropsy there was almost complete fibrosis of the atrioventricular node with focal fibrosis of the bundle of His and the bundle branches; rare focal myocarditis was also present. The other two patients survived after the insertion of pacemakers. Two patients with right bundle branch block also died and necropsy confirmed focal fibrosis of the bundle, again accompanied by mild focal myocarditis and fibrosis.[10]

CONTROL POPULATIONS

Control serum samples were obtained from the following groups: *(a)* 100 normal healthy individuals; *(b)* 70 pregnant women attending an antenatal clinic; *(c)* 100 patients with other neuromuscular illnesses (multiple sclerosis, 60; myasthenia gravis, 25; alcoholic myopathy, five; intervertebral disc lesions, 10).

DETECTION OF ANTIBODIES

Serum samples were stored at −70°C until use and then heat inactivated before testing. Antinuclear and anti-DNA antibodies were sought by standard indirect immunofluorescence techniques, with rat liver and *Crithidia luciliae* as the respective substrates.[11 12] Antibodies to soluble cellular antigens were detected by means of saline extracts of human spleen[13] (a potent source of the small ribosomal nucleoprotein, Ro antigen, as well as the other nucleoprotein complexes, Sm and nRNP) and fresh calf thymus, prepared as described for the human tissue.[13] For each extract the serum was screened first by double immunodiffusion[14] and then by counterimmunoelectrophoresis as outlined elsewhere.[15] In the latter technique, known control antisera were incorporated and all positive results were confirmed by the demonstration of a complete reaction of identity with one of these known controls.

Table 1 *Cardiac symptoms and electrocardiographic findings in 55 patients with polymyositis*

	No of cases (%)
Dyspnoea, angina, palpitation, and/or heart failure	27 (49)
Electrocardiographic abnormalities:	
Excluding conduction defects	19 (35)
With conduction defects	13 (24)
Total with clinical signs and symptoms and/or ECG findings	35 (64)

Table 2 *Detection of anti-Ro in 55 cases of polymyositis*

Patient group	*No of cases positive*
Polymyositis	33/55
Other neuromuscular diseases	1/100
Normal pregnant women	0/70
Normal healthy individuals	0/100

Positive anti-Ro antisera were obtained with the help of Dr P J Maddison, Dr G R V Hughes, and the Center for Disease Control, Atlanta; the CDC also supplied anti-La, anti-nRNP, and anti-Sm antisera (antisera to related non-histone extractable nuclear antigens).

The Ouchterlony plates were examined at 24, 48, 72, and 96 hours whereas the plates produced on counterimmunoelectrophoresis were left overnight at room temperature, washed in 5% citrate for four hours and then in phosphate buffered saline for 48 hours, and finally stained with Coomassie blue.

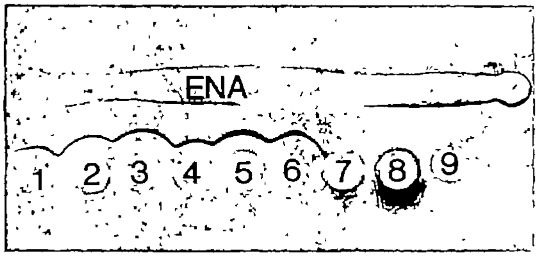

Figure *Counter immunoelectrophoresis with human spleen extract as the antigen source in the trough. Lines of identity are seen between positive anti-Ro antisera in wells 1–6. Wells 1 and 4 contain anti-Ro positive control antisera: wells 2, 3, 5, and 6 contain sera from four cases of polymyositis with complete heart block. Wells 7–9 contain negative sera from other patients with polymyositis. ENA, extractable nuclear antigens from spleen.*

Table 3 *Detection of anti-Ro in clinical subgroups of patients with polymyositis*

Subgroup	*No anti-Ro seropositive cases*
(I) Pure polymyositis	6/13
(II) Pure dermatomyositis	15/23
(III) Polymyositis/dermatomyositis associated with neoplasia	1/2
(IV) Juvenile polymyositis/dermatomyositis	2/6
(V) Polymyositis/dermatomyositis associated with connective tissue disease	9/11
Total	33/55 (60%)

Table 4 *Correlation between presence of anti-Ro and cardiac lesions in 55 cases of polymyositis*

Group	*No of cases positive (%)*
Patients with cardiac involvement	23/33 (69)
Patients with specific conduction damage	9/13 (69)
Patients with no evidence of cardiac involvement	10/22 (45)

Results

Table 2 shows that 33 (60%) of the 55 cases of polymyositis were seropositive for anti-Ro. The figure shows the positive results in four cases. One serum sample was anti-Ro positive in the control group of patients with other neuromuscular diseases; this patient had myasthenia gravis. Neither the normal pregnant women nor the healthy adult volunteers included any individuals with anti-Ro positive serum.

Table 3 shows the association of anti-Ro with the individual clinical subgroups. The highest percentage of anti-Ro positive sera (82%) was found in subgroup V—that is in patients in whom myositis was associated with another connective tissue disease. The next highest percentage was found in subgroup II (cases of dermatomyositis) in which 15 (65%) of 23 serum samples were positive. In subgroup I (pure polymyositis) almost half of the patients were seropositive for anti-Ro, while among the juvenile cases there were two patients with anti-Ro positive sera, and in the neoplasia subgroup there was one.

Table 4 shows how the serological findings correlated with evidence of cardiac involvement. Seventy per cent of cases with clinical or electrocardiographic signs of cardiac damage were anti-Ro positive and 69% of patients with electrocardiographic evidence of conduction defects were anti-Ro positive. Ten of 22 patients in whom there was no clinical or electrocardiographic evidence of heart damage were also anti-Ro positive. However, two of the patients were seen soon after (2 and 3 months) onset of disease, and involvement of the heart may be a late phenomenon. Also more detailed tests might have revealed cardiac damage in these 10 patients.

Finally, patients who had electrocardiographic evidence of conduction disorders shown on the electrocardiogram were analysed separately (table 5). In the patients with the most severe damage, which led to complete heart block, four of the five sera tested were anti-Ro positive. One of them was a man of 42 with dermatomyositis, who was anti-Ro seronegative when he was first examined three months after onset of disease. Two years later, when he complained of weakness and breathlessness and needed insertion of a pacemaker, he was seropositive. The fifth serum was anti-La positive; the presence of this antibody may, rarely, mask the simultaneous presence of anti-Ro.[16] Three of the four patients with first degree heart block had anti-Ro and two of the four with bundle branch block lesions associated with polymyositis were also anti-Ro seropositive. Of the 13 patients with conduction disorders, therefore, nine (possibly 10) were anti-Ro seropositive.

Tests for antibodies to the other non-histone nucleoprotein antigens La, nRNP, and SM showed that 13 of the anti-Ro seropositive patients were also positive for La antibodies while three patients had anti-La alone. Anti-nRNP was detectable in the four patients with the mixed connective tissue syndromes and anti-Sm in one other case. Two of the precipitating antibodies detected on the Ouchterlony plates could not be identified. Antinuclear antibodies were present at titres ranging from 1/64 (five cases) and 1/256 (three cases) to 1/1000 (eight cases). The serum samples with a titre of 1/1000 all gave a speckled appearance on immunofluorescence. No DNA antibodies were found and systemic lupus erythematosus was not diagnosed in any patient.

Discussion

We have shown in this study that 60% of a large group of patients with polymyositis and 69% of

Table 5 *Anti-Ro in patients with polymyositis and conduction disorders*

Conduction disorder	*No of anti-Ro seropositive cases*
Complete heart block	4/5
First degree heart block	3/4
Right bundle branch block	1/3
Left bundle branch block	1/3
Total	9/13 (69%)

those with associated cardiac damage had a antibody to tissue ribonucleoproteins (anti-Ro). Anti-Ro seropositivity is found in 0·1% of the normal population[17] so that it was approximately 700 times more common in these patients with polymyositis and heart lesions, including conduction defects. Four of five patients with complete heart block had anti-Ro and the fifth had a high titre of anti-La (an antibody whose presence may interfere with detection of anti-Ro).[16] Ten cases who were anti-Ro seropositive did not have clinical or electrocardiographic signs of heart damage. However, more sensitive methods of cardiac investigation would undoubtedly have revealed abnormalities, as has been shown conclusively in other series[3]; also heart damage tends to occur late.[5] Thus it is possible that the antibody is present for some time before the tissue injury develops.

Heart lesions were originally thought to be very uncommon in polymyositis, but since the 1970s a large number of clinical and necropsy reports have shown that from 70% to 100% of these patients will have evidence of cardiac damage and that cardiac failure is the third leading cause of death.[3–5] A whole range of heart abnormalities has been reported and damage to the conducting system results in various degrees of heart block in up to a third of patients.[3] Sudden unexpected deaths occur because of this damage and the cardiac lesions may progress even when the skeletal muscle lesions are improving.[5] This indicates the importance of identifying a possible marker (such as anti-Ro) for heart injury.

The cardiac lesions found in this disorder, and especially those affecting the conduction tissue, are the same in site, degree, and pathological features as those found in isolated complete congenital heart block.[6–8 10] This is why we thought that the same pathogenetic agent might be active in both conditions. There is strong evidence for the pathogenetic role of anti-Ro antibody in complete congenital heart block.[8 16 18 19] Concentrations of the Ro antigen, which has recently been purified and characterised[13] are highest in the heart and brain.[20] This may explain the susceptibility of cardiac tissue to such damage. Mothers of affected infants, however, do not appear to develop heart lesions.[16] An explanation for this is that only developing cardiac tissue is susceptible. The results of our study, however, show that adult cardiac cells can be severely damaged by anti-Ro. This may be because whereas the majority of the mothers are otherwise healthy, patients with polymyositis have such severe hormonal and cellular immunological abnormalities that, in the presence of these immune aberrations, cardiac myocytes and Purkinje fibres can be attacked. The HLA groups may also be important: anti-Ro was found in two of 10 cases of polymyositis associated with HLA-DR3.[21] Other factors are fluctuations in antibody titre, which we noticed in two of our cases, and the hormonal milieu. All our patients with dermatomyositis, of whom 65% were anti-Ro seropositive, were female. As in the large series of congenital heart block,[8] some of our patients also had antibodies to other soluble cellular antigens. Thirteen of the anti-Ro seropositive patients also had anti-La. Four anti-Ro seronegative patients had anti-RNP and one had anti-Sm.

An unexpected finding in our control group was that one of the 25 patients with myasthenia gravis, all of whom had heart disease associated with their myasthenia, was anti-Ro positive. These cases of myasthenia gravis were the subject of a recent review (J A Aarli, 1986, personal communication, and[22]). A larger series is now being examined to see whether anti-Ro is associated with cardiac damage in this other immune-mediated muscle disease.

Finally, to some extent our findings resemble those recently reported for a similar autoantibody, anti-Jo-1.[23] Anti-Jo-1 was found in 25% of patients with myositis alone; however, 68% of patients with myositis and pulmonary damage were seropositive. Anti-Jo-1 has therefore been suggested as a useful indicator of cryptogenic fibrosing alveolitis in patients with myositis.

Our results indicate that a specific autoantibody known to be associated with cardiac damage is 700 times more common in patients with polymyositis and heart involvement than in the general population. We suggest that this antibody (anti-Ro) is a marker for cardiac injury in myositis and may indeed be the pathogenetic agent. A search for anti-Ro in patients with myositis may help to identify those at risk of sudden death from cardiomyopathy.

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References

1 Mastaglia FL, Ojeda VJ. Inflammatory myopathies: Part 2. *Ann Neurol* 1985,17·317–23.

2 Behan WMH, Behan PO. Immunological features of polymyositis/dermatomyositis. *Springer Semin Immunopathol* 1985;8:267–93.

3 Askari AD, Huettner TL Cardiac abnormalities in polymositis/dermatomyositis. *Semin Arthritis Rheum* 1982;12:208–19.

4 de Vere R, Bradley WG. Polymyositis. its presentation,

morbidity and mortality. *Brain* 1975;**98**:637–66.

5 Stern R, Godbold JH, Chess Q, Kagen LJ. ECG abnormalities in polymyositis. *Arch Intern Med* 1984;**144**:2185–9.

6 Carter JB, Blieden LC, Edwards JE. Congenital heart block: anatomic correlations and review of the literature. *Arch Pathol* 1974;**97**:51–7.

7 Vetter VL, Rashkind WJ. Congenital complete heart block and connective tissue disease. *N Engl J Med* 1983;**309**:236–7.

8 Scott JS, Maddison PJ, Taylor PV, Esscher E, Scott O, Skinner RP. Connective-tissue disease, antibodies to ribonucleoproteins, and congenital heart block. *N Engl J Med* 1983;**309**:209–12.

9 Bohan A, Peter JB. Polymyositis and dermatomyositis. *N Engl J Med* 1975;**292**:344–7; 403–7.

10 Behan WMH, Aitchison M, Behan PO. Pathogenesis of heart block in a fatal case of dermatomyositis. *Br Heart J* 1986;**56**:479–82.

11 Holborow EJ, Weir DM, Johnson GD. A serum factor in lupus erythematosus with affinity for tissue nuclei. *Br Med J* 1957;**ii**:732–4.

12 Aarden LA, de Grott ER, Feltkamp TEW. Immunology of DNA. III. *Crithidia luciliae:* a simple substrate for the determination of anti-dsDNA with the immunofluorescence technique. *Ann NY Acad Sci* 1975;**254**.505–14.

13 Venables PJW, Smith PR, Maini RN. Purification and characterization of the Sjogren's syndrome A and B antigens. *Clin Exp Immunol* 1983;**54**:731–8.

14 Venables PJW, Mumford PA, Maini RN. Antibodies to nuclear antigens in polymyositis: relationship to autoimmune "overlap syndromes" and carcinoma. *Ann Rheum Dis* 1981;**40**:217–23.

15 Bunn CC, Gharavi AE, Hughes GRV. Antibodies to extractable nuclear antigens in 173 patients with DNA-binding positive SLE: an association between antibodies to ribonucleoproteins and Sm antigens observed by counter immunoelectrophoresis. *J Clin Lab Immunol* 1982;**8**:13–7.

16 Lee LA, Weston WL. New findings in neonatal lupus syndrome. *Am J Dis Child* 1984;**138**:233–6.

17 Tan EM. Autoantibodies to nuclear antigens (ANA): their immunobiology and medicine. *Adv Immunol* 1982;**233**:167–241.

18 Litsey SE, Noonan JA, O'Connor WM, Cottrill CM, Mitchell B. Maternal connective tissue disease and congenital heart block. *N Engl J Med* 1985; **312**:98–100.

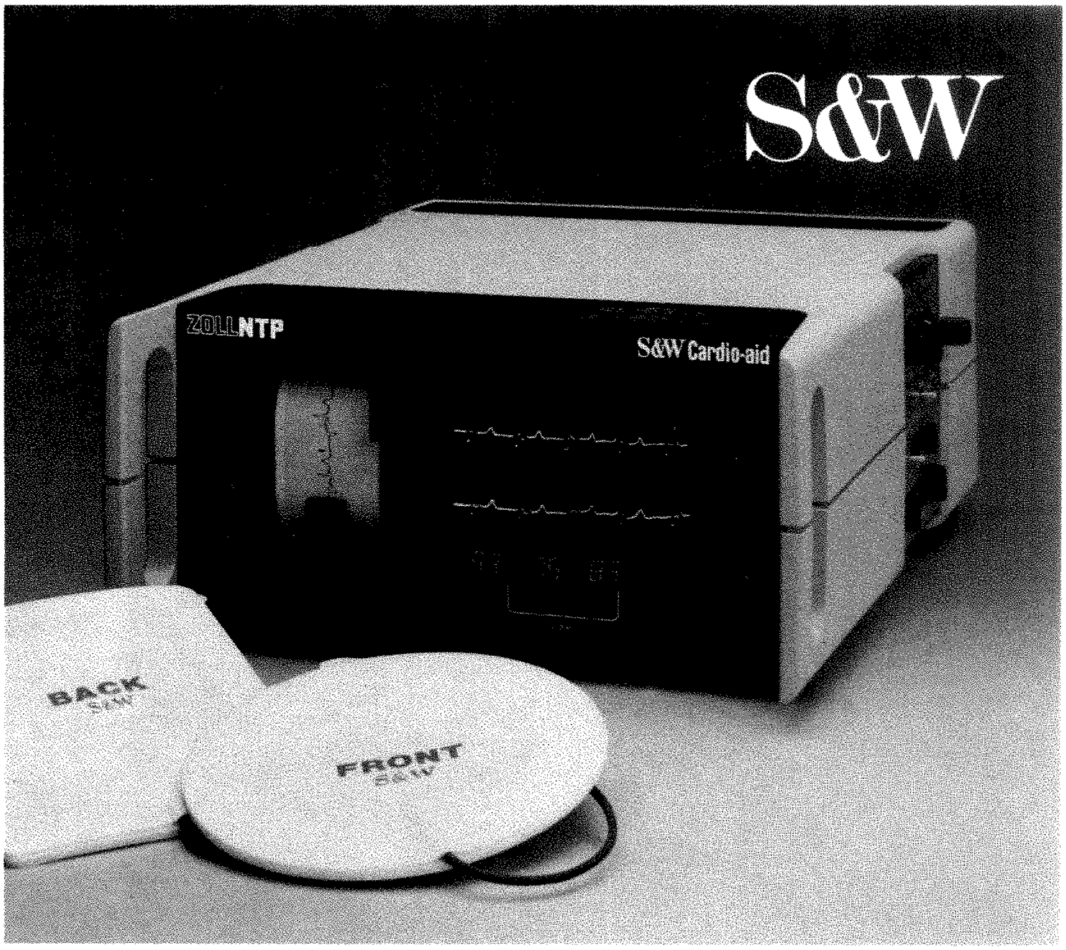
19 Taylor PV, Scott JS, Gerlis LM. Maternal connective tissue disease and congenital heart block [Letter]. *N Engl J Med* 1985;**312**:1328–9.

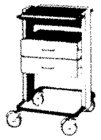
20 Wolin SL, Steitz JA. The Ro small cytoplasmic ribonucleoproteins: identification of the antigenic protein and its binding site on the Ro RNAs. *Proc Natl Acad Sci USA* 1984;**81**:1996–2000.

21 Arnett FC, Hirsch TJ, Bias WB, Nishikai M, Reichlin M. The Jo-1 antibody system in myositis: relationships to clinical features and HLA. *J Rheumatol* 1981;**8**:925–30.

22 Hofstad H, Ohm O-J, Mark SJ, Aarli JA. Heart disease in myasthenia gravis. *Acta Neurol Scand* 1984; **70**:176–84.

23 Bernstein RM, Morgan SH, Chapman J, *et al.* Anti-Jo-1 antibody; a marker for myositis with interstitial lung disease. *Br Med J* 1984;**289**:151–2.

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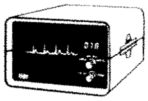
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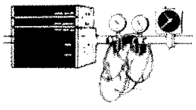
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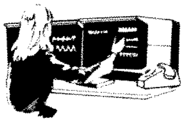
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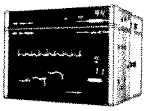
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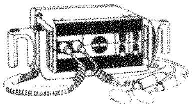
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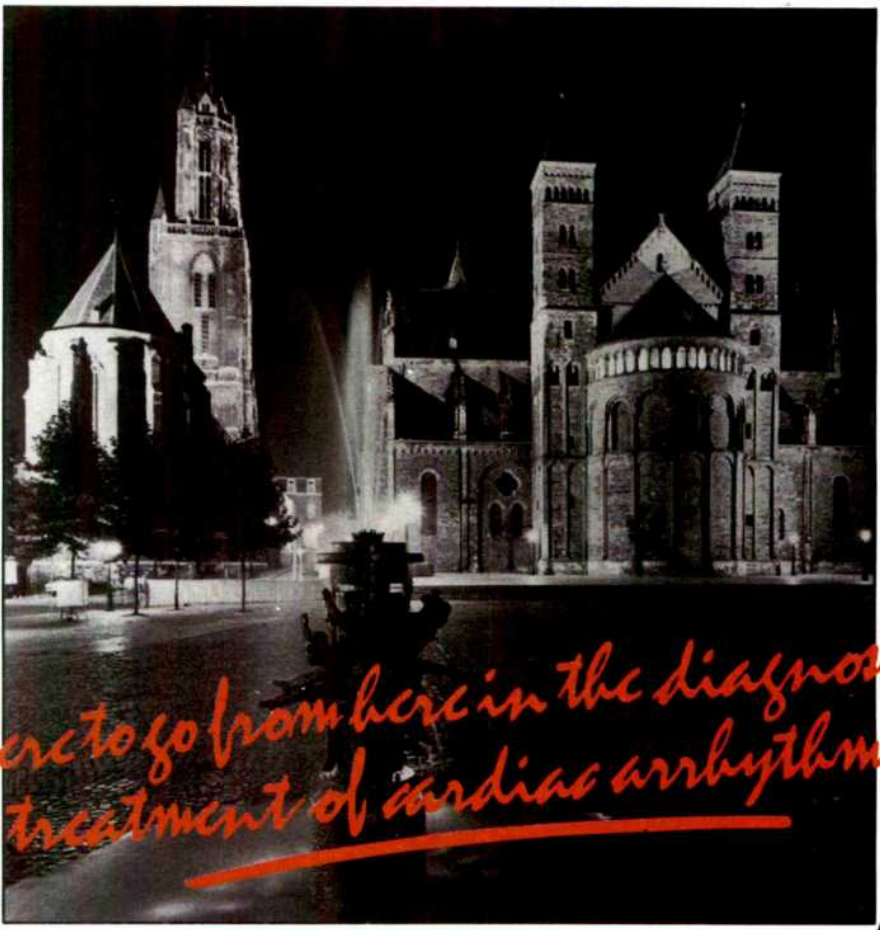

"Where to go from here in the diagnosis and treatment of cardiac arrhythmias"

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Br Heart J 1987;57:181–3

Dilated cardiomyopathy associated with haemolytic uraemic syndrome

J POULTON,* C M TAYLOR,† J V DE GIOVANNI*

*From the Departments of *Cardiology and †Nephrology, The Children's Hospital, Ladywood, Birmingham*

SUMMARY In two children with the haemolytic uraemic syndrome dilated cardiomyopathy occurred in the absence of hypertension, or fluid or electrolyte disturbance. These cases presented with acute left ventricular failure. Echocardiography showed left ventricular dilatation and reduced contractility. There was also ventricular wall thickening, which persisted. Twelve other children with haemolytic uraemic syndrome had prospective echocardiography. Eleven of them showed no evidence of cardiomyopathy and in one transient dilatation and reduced contractility developed without clinical signs.

Dilated cardiomyopathy is a rare but important extrarenal manifestation of the haemolytic uraemic syndrome and is best demonstrated by echocardiography.

Extrarenal manifestations of haemolytic uraemic syndrome are increasingly recognised and are responsible for much of the mortality and long term morbidity of the disorder.[1] The following cases establish that congestive cardiomyopathy can be a complication of the haemolytic uraemic syndrome. This complication is readily confirmed by echocardiography.

Patients and methods

CASE 1

A 21 month old girl was admitted after nine days of bloody diarrhoea. Examination showed slight peripheral oedema; the heart rate was 110 beats/min, the respiratory rate 30 per minute, and blood pressure was 125/80 mm Hg. Haemolytic uraemic syndrome was diagnosed on the basis of the following features: microangiopathic anaemia (haemoglobin 8 g/dl with schistocytes and burr cells), thrombocytopenia (platelet count 100 × 10^9/l), and oliguric renal failure (plasma creatinine 783 μmol/l). Peritoneal dialysis was performed from the third to twenty first day after admission. Apart from the admission measurement blood pressure remained in the normal range without treatment. On the fifty sixth day left ventricular failure developed. An electrocardiogram and a chest *x* ray were performed for the first time at this stage of the illness; the former showed non-specific transient T wave changes and the *x* ray showed global cardiomegaly and pulmonary oedema. Echocardiography showed a dilated left ventricle with increased mural thickness and global functional impairment. The ventricular septal thickness measured 0·7 cm (normal (mean (SD)) 0·47 (0·09) cm) and the left ventricular posterior wall 0·66 cm (normal 0·45 (0·09) cm). She was treated with frusemide and digoxin. Subsequently the blood pressure rose to 140/90 mm Hg and was satisfactorily controlled thereafter with methyldopa.

Histological examination of a renal biopsy specimen obtained on the fifty second day showed total sclerosis in 60% of glomeruli, atrophy of the capillary tufts in many of the remainder, and considerable tubular atrophy. Intimal proliferation and medial hypertrophy were seen in small and medium sized arteries.

At one year follow up the child had stable chronic renal failure and moderate proteinuria. The figure shows echocardiographic measurements over this period. The left ventricular diastolic dimension returned to normal but left ventricular function remained abnormal and mural thickness continued to be above the normal range. The chest *x* ray was normal. Digoxin was discontinued after a year and she continued to be treated for hypertension.

Requests for reprints to Dr J V De Giovanni, Department of Cardiology, The Children's Hospital, Ladywood Middleway, Ladywood, Birmingham B16 8ET.

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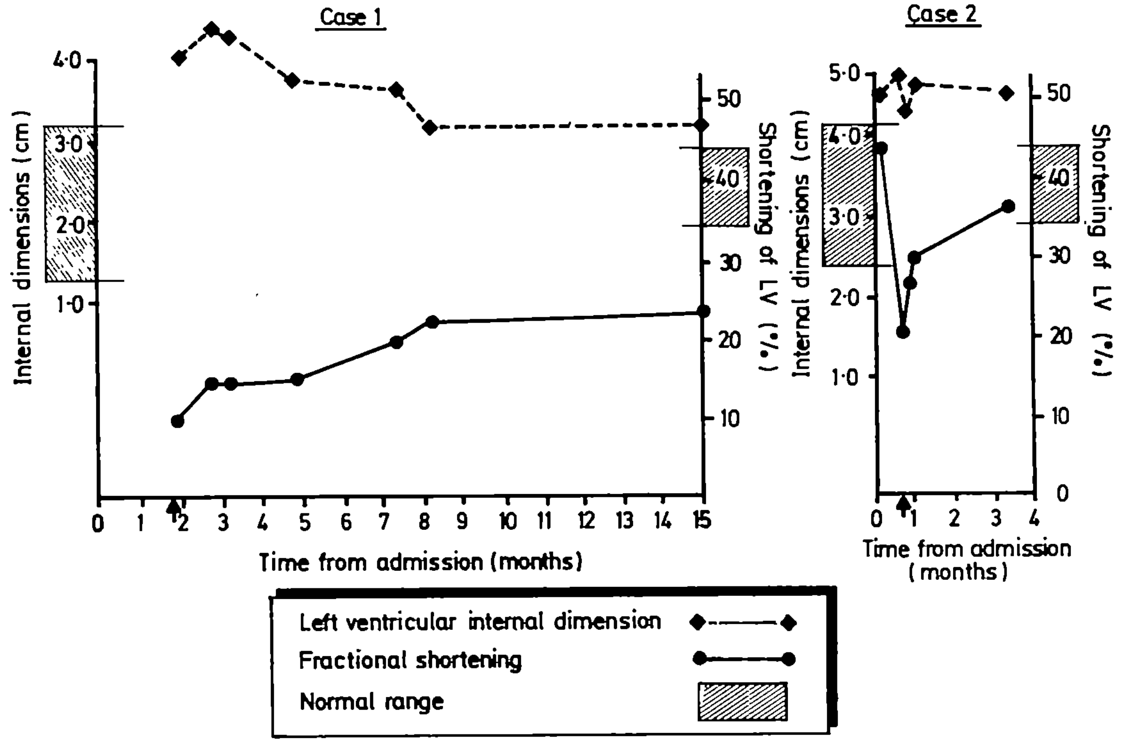

Figure *Left ventricular (LV) dimension and fractional shortening derived from serial echocardiograms in cases 1 and 2. Arrow indicates onset of pulmonary oedema.*

CASE 2

An eight year old boy presented with headaches, lethargy, and vomiting for two weeks and bruises and haematuria for three days. On examination his pulse was 120 beats/min, blood pressure 120/65 mm Hg, and he had a purpuric rash. Haemolytic uraemic syndrome was diagnosed because acute renal failure, microangiopathic anaemia, and thrombocytopenia were present. Over the next 14 days he progressed to end stage renal failure and was thereafter maintained on chronic peritoneal dialysis. On the sixteenth day his blood pressure was labile between 115/80 and 150/110 mm Hg. This was promptly treated with a β blocker. About this time a transient left partial hemiparesis developed and he had two focal convulsions.

The echocardiogram on admission showed slight ventricular dilatation, consistent with anaemia, and slight fluid overload but normal function. The electrocardiogram showed voltage changes consistent with left ventricular hypertrophy. On the twenty first day after admission acute pulmonary oedema developed. Serial echocardiograms showed slight dilatation of the left ventricle but there was a considerable reduction in ventricular function (figure). These abnormalities persisted despite a change in the antihypertensive treatment from a β blocker to captopril. Throughout this period his fluid and electrolyte balance was well controlled by peritoneal dialysis. Unlike case 1 his left ventricular contractility returned to normal within four months.

In both cases serological tests for eleven common viruses, including six types of Coxsackie B, were negative.

After our experience with case 1, all patients with haemolytic uraemic syndrome underwent prospective echocardiography during their acute illness. In addition to the two cases described above, twelve other children were examined. Eleven had no evidence of cardiomyopathy. In one child minor and transient dilatation and a reduction in contractility developed without clinical signs.

Discussion

As in other forms of acute renal failure, the cardiac complications of haemolytic uraemic syndrome are usually secondary to volume overload, hypertension, and hyperkalaemia. Although hypertension was seen in cases 1 and 2 it was unrelated to the onset of cardiac dilatation. It occurred after demonstration of poor left ventricular function in case 1 and was transient and not severe in case 2. Cardiomyopathy is not a feature of acute renal failure but it may be seen in end stage disease. Myocarditis has been described in two children with haemolytic uraemic syndrome whose illness appeared to be precipitated by Coxsackie B infection.[2] In our patients none of these recognisable factors offers an explanation for the cardiomyopathy and although myocarditis is unlikely it cannot be entirely excluded. Although we could not rule out the possibility that a separate disease process was responsible for the cardiomyopathy, the temporal relation with haemolytic uraemic syndrome suggested that this disease was a more probable cause.

Extrarenal manifestations in haemolytic uraemic syndrome are becoming more clearly defined.[3 4] Some histological studies have identified microvascular obstruction caused by endothelial swelling and intravascular thrombus with local myocardial ischamia.[1] It appears from our experience and a past report,[5] however, that previously unexplained left ventricular failure may occur several weeks after the resolution of the blood film abnormalities. It is therefore difficult to relate the cardiomyopathy to the acute microvascular obstruction.

In cases 1 and 2 echocardiography showed that myocardial impairment improved slowly with time and that ventricular dilatation and hypertrophy persisted. Furthermore, echocardiography was capable of identifying cardiac abnormalities in the absence of either physical or radiological signs and is therefore the investigation of choice. Despite the rarity of cardiac involvement, routine echocardiographic screening of children with haemolytic uraemic syndrome should be performed because of the important clinical implications for the management of hypertension and for prognosis.

References

1 Upadhaya K, Barwick K, Fishaut M, Kashgarian M, Seigel NJ. The importance of nonrenal involvement in haemolytic uraemic syndrome. *Pediatrics* 1980;65:115–20.

2 Ray CG, Portman JN, Stanton SJ. Haemolytic uraemic syndrome. *Am J Dis Child* 1971;122:418–20

3 Fong FSC, de Chadarevian JP, Kaplan BS. Hemolytic uremic syndrome: current concepts and management. *Pediatr Clin North Am* 1982;29:835–53.

4 Gianantonio CA. Extrarenal manifestations of the hemolytic uremic syndrome. In: Strauss J, ed. *Acute renal disorders and renal emergencies* Boston. Martinus Nijhoff, 1984:43–50

5 Lieberman E. Hemolytic-uremic syndrome. *J Pediatr* 1972;80:1–16.

Br Heart J 1987;57:184–7

Reversed offsetting of the septal attachments of the atrioventricular valves and Ebstein's malformation of the morphologically mitral valve

MAURICE LEUNG,* MICHAEL L RIGBY,* ROBERT H ANDERSON,*
RICHARD K H WYSE,† FERGUS J MACARTNEY†

*From the *Brompton Hospital and †Hospital for Sick Children, London*

SUMMARY Ebstein's anomaly of the tricuspid valve is characterised by downstream displacement of the tricuspid leaflets. In the case of the septal leaflet, the result is exaggerated offsetting of the atrioventricular valves. Thus it might be supposed that in Ebstein's anomaly of the mitral valve, downstream displacement of the aortic (septal) leaflet of the mitral valve could move its attachment beyond that of the tricuspid valve, resulting in reversed offsetting. To examine this hypothesis three patients each with a concordant atrioventricular connection were studied. The first, with Marfan's syndrome and without an abnormal mitral valve, had reversed offsetting shown by echocardiography. The second, without Marfan's syndrome and with Ebstein's anomaly of the mitral valve, showed echocardiographically normal offsetting but a displaced mural leaflet. The third, in whom Ebstein's anomaly of the mitral valve was confirmed at necropsy, showed all the features of the second case, with normal offsetting of the atrioventricular valves.

Thus reversed offsetting is not a feature of Ebstein's anomaly of the mitral valve and in the first case this feature was caused by upward displacement of the tricuspid valve secondary to dilation of the aortic root.

In hearts with the usual atrial arrangement (solitus) and concordant atrioventricular connection, four chamber echocardiographic sections show that the septal attachment of the mitral valve is usually closer to the atria than the septal attachment of the tricuspid valve. The detection of mirror image arrangement of this anticipated offsetting of the atrioventricular valves in hearts with the usual atrial arrangement has, when the septal structures are intact, been described as a significant finding in some hearts with discordant atrioventricular connection.[1-3] We have encountered this reversal of the normal offsetting of the atrioventricular valves in the presence of concordant atrioventricular and ventriculoarterial connections with the usual atrial arrangement. This suggested to us the diagnosis of Ebstein's anomaly of the left sided mitral valve, a rare but well recognised lesion.[4 5] Subsequent examination of a necropsy example of this malformation together with a case examined echocardiographically showed that this lesion does not produce reversed offsetting. When considered in terms of the arrangement of the normal mitral valve, this is to be expected. The findings in the initial case were subsequently shown to be due to enlargement of the aortic root in the setting of Marfan's syndrome.

Patients and heart studied

The first patient was born at 34 weeks' gestation weighing 1·9 kg and was delivered by caesarean section because of maternal toxaemia of pregnancy. The early neonatal period was complicated by severe hyaline membrane disease and persistent fetal circulation requiring intermittent positive ventilation for 10 days and tolazoline infusion for three days. After extubation the infant remained tachypnoeic. At seven weeks severe heart failure had developed and he was failing to thrive. During this time he was pink with normal peripheral pulses. There was leftward displacement of the cardiac apex and a prominent precordial impulse. A grade 4/6 pansystolic murmur

Requests for reprints to Professor Robert H Anderson, Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, Fulham Road, London SW3 6HP.

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and a grade 2/6 mid-diastolic rumble were audible at the apex. He was also noted to have dysmorphic features with a high arched palate and elongated fingers. The electrocardiogram showed sinus rhythm with a normal precordial R/S progression pattern for age. The chest radiograph showed a mild degree of pulmonary venous congestion with slight enlargement of heart size.

Cross sectional echocardiography showed a symmetrical arrangement of the inferior caval vein and abdominal aorta with the former to the right, indicating usual atrial arrangement (situs solitus). The usual offsetting of the atrioventricular valve was reversed in the apical four chamber section (fig 1), but the left sided ventricle was of a morphologically left pattern and the left valve was a typical mitral valve. There was moderate prolapse of both leaflets of the valve with enlargement of the left atrium. The ventriculoarterial connection was concordant and the great arteries were normally related. The aortic root was noted to be grossly dilated. Cardiac catheterisation excluded an intracardiac shunt and selective left ventriculograms showed mitral regurgitation and confirmed the presence of severe dilation of the aortic root. An initial diagnosis of Ebstein's anomaly of the mitral valve was considered because of the results of cross sectional echocardiography. This was not the case (see below). Instead, the reversed offsetting was the consequence of the severely dilated aortic root caused by Marfan's syndrome.

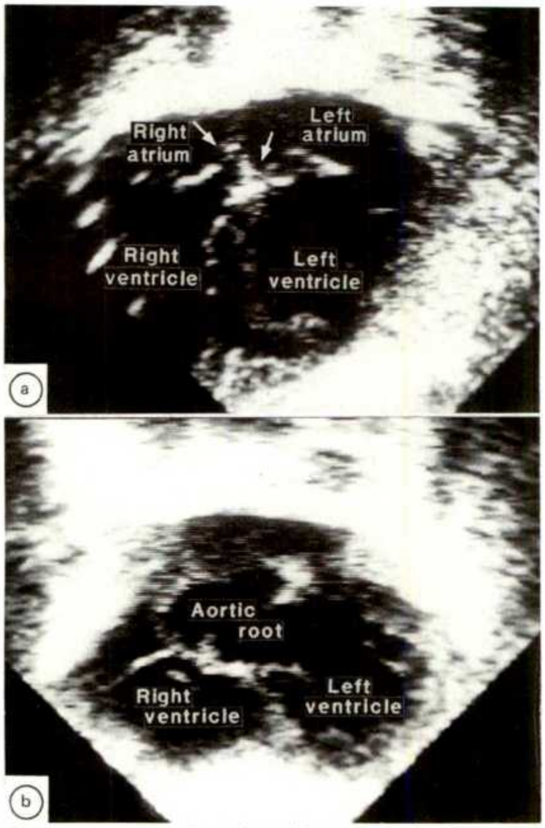

Fig 1 *A four chamber echocardiogram (a) showing reversed offsetting of the septal attachments of the atrioventricular valves in a patient with usual atrial arrangement and concordant atrioventricular connection. The patient was also shown (b) to have gross dilatation of the aortic root. The diagnosis was Marfan's syndrome.*

Subsequently we encountered a child who was shown during life to have Ebstein's malformation of the morphologically mitral valve. He presented with a heart murmur at six weeks of age and by four months became cyanosed when he cried and he was tachypnoeic. Cardiac catheterisation at the referring centre showed a normal atrial arrangement, a concordant atrioventricular connection, and double outlet right ventricle with a subaortic ventricular septal defect, pulmonary arterial and venous hypertension (mean left atrial pressure 30 mm Hg), and mitral regurgitation. The child was referred to the Hospital for Sick Children, Great Ormond Street, London at six months of age. Cross sectional echocardiogram demonstrated normal offsetting of the proximal septal attachments of the atrioventricular valves (fig 2a). The mural leaflet of the mitral valve, however, was grossly displaced towards the apex of the left ventricle (fig 2b). The mitral regurgitation, confirmed at catheterisation, was therefore a consequence of Ebstein's malformation of the morphologically mitral valve. The child was treated by banding of the pulmonary trunk and Blalock-Hanlon septectomy. This was successful and he was discharged home 10 days later and has done well for the past three years.

We had previously studied a heart from the Cardiopathological Museum of the Hospital for Sick Children, Great Ormond Street, London, which had been the arbiter of appropriate echocardiographic diagnosis during life. The atrial arrangement and chamber connections were all normal. The salient anatomy concerned the left atrioventricular valve. Although this was of a basically mitral pattern, the anatomy was more unusual. The aortic (anterior) leaflet of the valve was, as expected, in fibrous continuity with the aortic valve, but it showed a partial arcade lesion, the papillary muscles being continued as a muscular ridge along the leading edge of the valve leaflet. The mural aspect of the valve was grossly distorted, being densely adherent to the pariental wall of the ventricular inlet with no true delamination of leaflet tissue (fig 3). There was

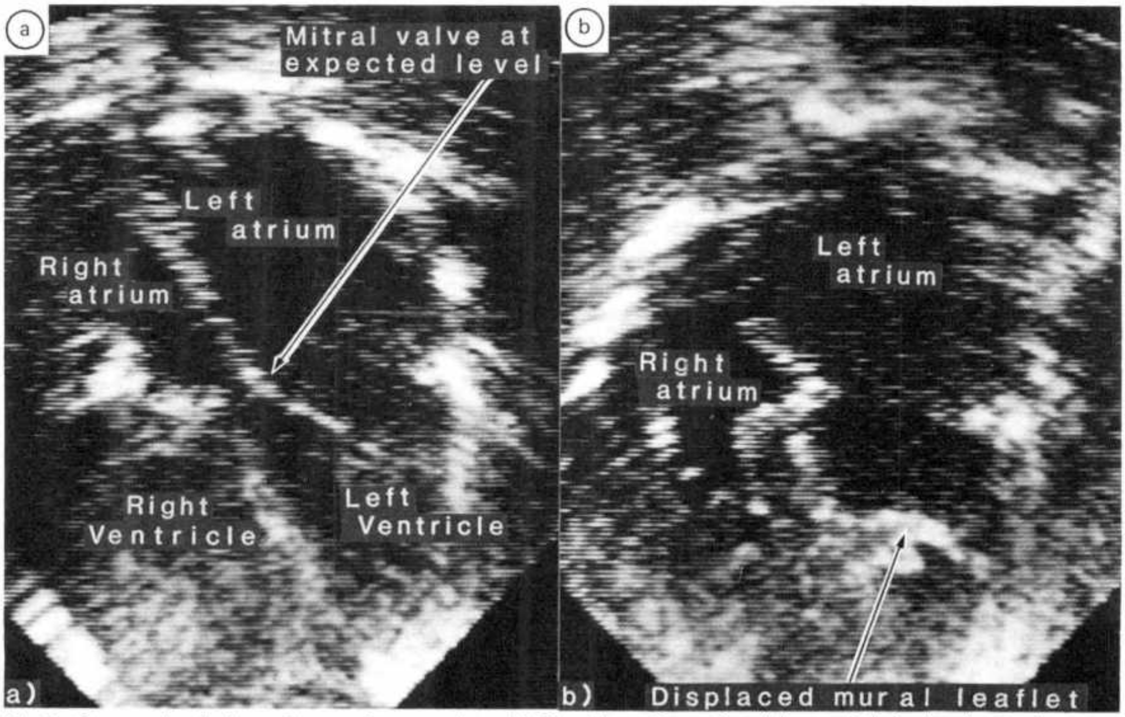

Fig 2 *Cross sectional echocardiograms from a patient with Ebstein's malformation of the morphologically mitral valve showing (a) the normal offsetting of the atrioventricular valves and (b) the downward displacement of the mural leaflet.*

no tension apparatus present for this part of the valve. The appearance was similar to that of Ebstein's anomaly of the morphologically tricuspid valve. In Ebstein's anomaly of the tricuspid valve, however, it is displacement of the septal leaflets that results in exaggerated offsetting of the annular attachment at the level of the atrioventricular septum. The mural rather than the septal leaflet of the mitral valve was found to be affected in this case. A four chamber section cut through the heart (fig 3b) showed that the aortic leaflet of the valve was attached at the expected position. The displaced segment of the valve was exclusively attached to the parietal wall of the ventricular inlet component. There was not, therefore, any reversal of the offsetting in the region of the atrioventricular septum.

Discussion

Reversed offsetting of the normal atrioventricular valve attachments in the setting of usual atrial arrangement (solitus) should alert the echocardiographer to the possibility of a discordant atrioventricular connection. A scan along the inlet ventricular septum will then demonstrate the attachment of the tension apparatus of the atrioventricular valves. The septal leaflet of the morphologically tricuspid valve always has multiple attachments to the inlet septum. This is in contrast with the mitral valve tension apparatus which is attached to the paired papillary muscles away from the septum. A distinct cleavage plane is always found between valve and septum on the morphologically left side.

The use of these criteria, along with those of others usually used for ventricular identification, made it easy to demonstrate the presence of a concordant atrioventricular connection in our initial case. It was then tempting to propose that the reversed valvar offsetting was due to the rare abnormality of Ebstein's malformation of the morphologically mitral valve, particularly since the valve was known to be regurgitant. The morphology of this condition has been described by Ruschhaupt *et al*[4] and we have seen both the case reported here (which has been illustrated elsewhere[5]) and a further case in the collection of Children's Hospital of Pittsburgh, USA. All of these show that it is the mural leaflet of the mitral valve rather than the aortic leaflet that is displaced into the left ventricle. This necropsy finding was subsequently confirmed in life by echocardiography of our second case. The arrangement is to be expected, since the aortic leaflet of the mitral valve, as its name suggests, is in fibrous continuity with the aortic valve. It spans the inlet-

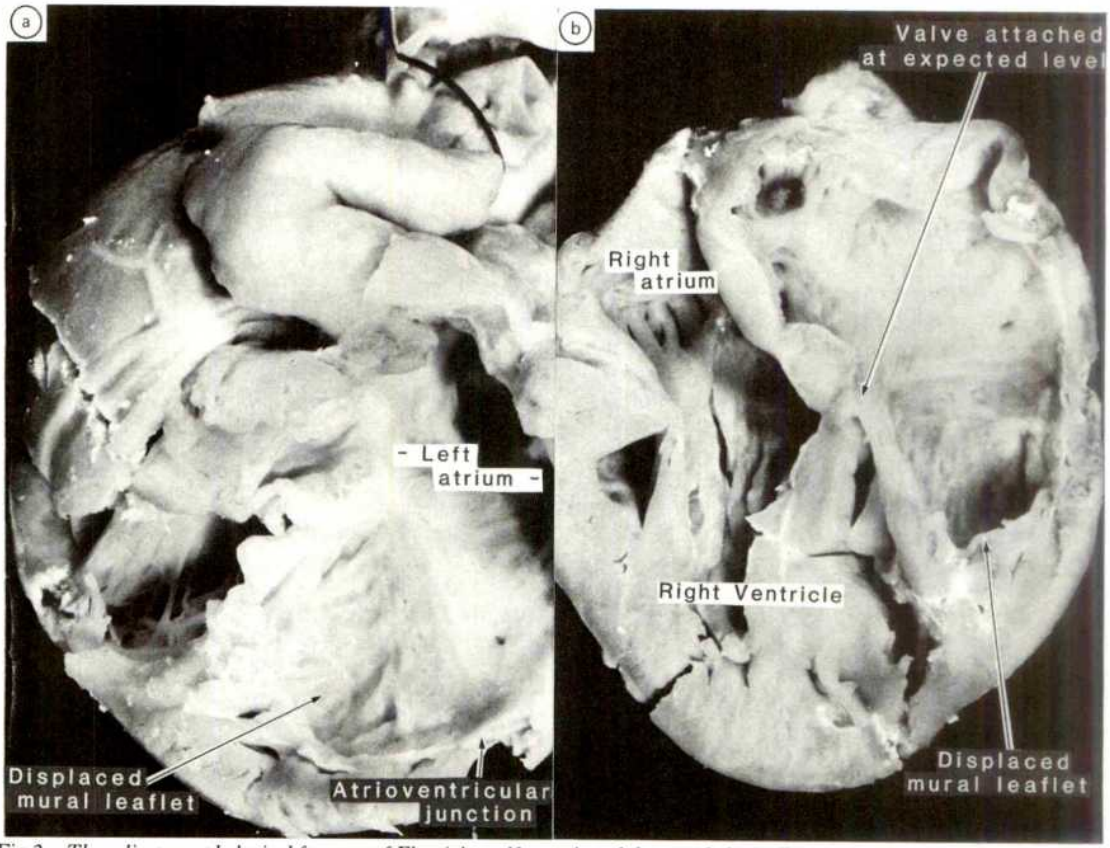

Fig 3 *The salient morphological features of Ebstein's malformation of the morphologically mitral valve. (a) Shows the opened valve, the mural leaflet being downwardly displaced. The four chamber section (b) shows that the valve retains its expected level of attachment at the atrioventricular septum.*

outlet junction of the left ventricle and cannot be displaced along the parietal wall or septum because it is not related to either of these structures. Therefore, apical displacement of the mitral valve leaflet was not the explanation for the echocardiographic features in our first patient. Rather it was upward displacement of the leaflets of the tricuspid valve by the dilated aortic root. The appropriate diagnosis is Marfan's syndrome.[6] This is supported both by the dysmorphic features of the patient and the presence of prolapse of both leaflets of the mitral valve. In contrast, in the second case the mitral regurgitation was indeed due to Ebstein's malformation of the morphologically tricuspid valve. To the best of our knowledge this is the first non-invasive diagnosis of this rare lesion.

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References

1 Foale R, Stefanini L, Rickards A, Somerville J. Left and right ventricular morphology in complex congenital heart disease defined by two dimensional echocardiography. *Am J Cardiol* 1982;**49**:93–9.
2 Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional real-time ultrasonic imaging of the heart and great vessels. Technique, image orientation, structure identification, and validation. *Mayo Clin Proc* 1978;**53**:271–303.
3 Sutherland GR, Smallhorn JF, Anderson RH, Rigby ML, Hunter S. Atrioventricular discordance: cross-sectional echocardiographic—morphological correlative study. *Br Heart J* 1983;**50**:8–20.
4 Ruschhaupt DG, Bharati S, Lev M. Mitral valve malformation of Ebstein type in absence of corrected transposition. *Am J Cardiol* 1976;**38**:109–12.
5 Becker AE, Anderson RH. *Pathology of congenital heart disease*. London: Butterworths, 1981:149–51.
6 Sisk HE, Zakha KG, Pyeritz RE. The Marfan syndrome in early childhood: analysis of 15 patients diagnosed at less than 4 years of age. *Am J Cardiol* 1983;**52**:353–8.

Br Heart J 1987;57:188–9

The British Cardiac Society Working Group* on Coronary Prevention: conclusions and recommendations

The Working Group was appointed by the British Cardiac Society to make recommendations on reduction of coronary heart disease primarily to cardiologists, general physicians, and general practitioners but also to related professionals and, where relevant, to health service administrators and government. It was instituted in October 1985 and has met six times.

Conclusions and recommendations

Coronary heart disease is complex and multifactorial in origin. The recommendations aimed at its reduction put forward in this report are based on the weight and consistency of the evidence and the likely balance of benefit and harm. They cannot be based on certainty of effectiveness.

Coronary heart disease is a widespread and common disease. It is the greatest single cause of death in the United Kingdom, leading to one third of all deaths in men and a quarter of all deaths in women. Mortality is higher than in most other countries, with particularly high rates in Scotland, Northern Ireland, and Wales.

There has been a small decline in mortality from coronary heart disease in England, Wales, and Scotland since 1979 and this is most evident in men aged 35–44 years. It is likely that this favourable trend is related more to changes in incidence of the disease than to reduction in case fatality. While it is not possible to identify the specific influences that may be responsible, reduction of cigarette smoking and a healthier diet have probably contributed.

We recognise, however, that multifactorial intervention trials have not fulfilled their hopes, although the results of trials of lowering raised blood cholesterol or raised blood pressure in those at special risk are encouraging. We also recognise that coronary atherosclerosis in adults has not yet been shown convincingly to regress and that other pathogenic processes leading to coronary heart disease, such as thrombosis and plaque fissure, may not be influenced greatly by control of the three main coronary risk factors—cigarette smoking, raised blood cholesterol, and raised blood pressure. It is unlikely, therefore, that coronary heart disease will be prevented wholly by control of these risk factors. Nevertheless, there is very strong circumstantial evidence from many experimental, biochemical, and epidemiological studies that the disease should be preventable. We, therefore, endorse fully the principles put forward in 1976 by the Joint Working Party of the Royal College of Physicians of London and the British Cardiac Society and recommend that cardiologists in particular, and the medical profession in general, should implement the following health measures.

SMOKING

Every opportunity should be taken to influence the population—and central and local authorities—to eliminate cigarette smoking, particularly in young people.

CHOLESTEROL

Those with blood cholesterol concentrations above 6·5 mmol/l (250 mg/dl) should be given dietary advice. This may need to be combined with drug treatment when the concentrations are greater than 7·8 mmol/l (300 mg/dl). The aim should be to lower total cholesterol towards 5·2 mmol/l (200 mg/dl). This is particularly important for young men.

DIET

So far as specific dietary advice is concerned, we endorse the most recent recommendations from the Panel on Diet in Relation to Cardiovascular Disease (Committee on Medical Aspects of Food Policy: Diet and Cardiovascular Disease (1984)). The consumption of fat in the United Kingdom should be reduced so that no more than 35% of food energy comes from total fat and 15% of food energy from saturated fatty acids. The ratio of polyunsaturated fatty acids to saturated fatty acids (the P:S ratio) should be increased to 0·45. The more stringent recommendations of the Expert Committee of the

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The full Report is published as a separate booklet that can be obtained from the British Cardiac Society, 7 St Andrew's Place, Regent's Park, London NW1 4LB.

**Composition of Working Group:* G H Fowler, General Practitioner, Oxford; B J Kirby, Cardiologist, Exeter; J G G Ledingham, Consultant Physician, Oxford; M G Marmot, Epidemiologist, London; M F Oliver, Cardiologist, Edinburgh (Convener).

World Health Organisation (1982) that energy from total fat should be limited to 30% of food energy and energy from saturated fats to 10% of food energy are not recommended for the general population at the present time but these limits are appropriate for individuals at special risk of coronary heart disease. The consumption of fibre rich carbohydrates should be increased to compensate for the reduced intake of fat. The dietary intake of common salt should be decreased.

BLOOD PRESSURE

Lowering of raised blood pressure by drug treatment has not been shown convincingly to reduce the incidence of myocardial infarction, though the beneficial effects of treatment on the incidence of stroke and cardiac failure are undoubted. Those with diastolic pressures above 100 mm Hg require treatment and attention to other risk factors.

OBESITY

This should be avoided in adults and in children by a combination of appropriate food intake and regular exercise.

EXERCISE

Physical activity should be encouraged as a normal part of daily living.

CHILDREN'S DIET

Particular attention should be given to the provision of a healthy diet, as outlined above, to children over the age of five.

In order to implement these recommendations, cardiologists, consultant physicians, general practitioners, health authorities, and related professionals must assume a more active role than in the past. We recommend, therefore, that:

(*a*) *Cardiologists* should give the lead in establishing a really effective policy, particularly in their regions, to prevent and reduce coronary heart disease. The practice of clinical cardiology should include preventive measures for individuals at special risk. Collectively, through the British Cardiac Society, they should advise central and local government on the most effective ways of preventing the disease. To ensure that up to date advice is provided, reports should be issued by the British Cardiac Society at intervals of not more than five years.

(*b*) *General practitioners* should be more active in the prevention of coronary heart disease. There are many opportunities for health promotion and disease prevention in daily practice and for seeking those with a high risk for coronary heart disease. A key asset for general practitioners is their access to families: vascular diseases often run in families and yet this knowledge is poorly used for preventive purposes. There is already a very large measure of agreement of what should be done. This needs to be emphasised, since inappropriate prominence is often given to areas of controversy.

(*c*) *Health authorities* should recognise their potential in the prevention of coronary heart disease and incorporate prevention into planning and delivery of health services. Cardiologists and general practitioners should collaborate with community physicians and health education officers in heart disease prevention teams in every district and ensure that adequate resources are provided.

(*d*) The *media* should be informed more purposefully. Cardiologists (in particular), epidemiologists, and all doctors concerned with health education need to make a more coordinated and sustained effort to guide the media with accuracy, judgement, and responsibility towards effective prevention of coronary heart disease.

(*e*) The need for more *research* has received little attention from most of the national and international reports of the last ten years. We do not yet have all the answers to the prevention of coronary heart disease and more basic clinical and epidemiological studies are essential. Government should recognise these deficiencies in knowledge and provide funds to support more investigation as part of its overall programme for the prevention of coronary heart disease.

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Did Einthoven invent a string galvanometer?

HOWARD B BURCHELL

From the Cardiovascular Division, University of Minnesota School of Medicine, Minneapolis, USA

Clinical electrocardiography belongs wholly to this century and stems from a paper of Willem Einthoven "Un nouveau galvanomètre" in 1901.[1] The epochal work of Waller in 1887,[2] which showed that in man cardiac potentials could be recorded, had aroused Einthoven's interest and he devoted a large part of the next three decades to perfecting high fidelity methods of studying these potentials with instruments of his design.

In a recent review paper Cooper[3] opined that Einthoven did not invent the string galvanometer and invited the inference that Einthoven did not give proper priority and credit to Ader. This raises semantic problems regarding the word "invent" and casts doubts on the veracity of Einthoven's account of his own work. It is not a new controversy and undoubtedly some writers, historically minded but not necessarily historical scholars, have used the word "invent" loosely. The hearsay opinion has been repeated in the literature: that Einthoven had his instrument built just by adapting already known equipment to his purpose. For instance, Barker (1910) in a long paper extolling the great clinical possibilities of electrocardiography, states "Einthoven of Leyden devised his string galvanometer based upon the suggestions of Ader."[4]

My argument endorsing the propriety of the use of the word "invent" for Einthoven's instrument is based on the following points. The meaning of any word is defined by its common use. When a person does something in a new and effective way he is said to be inventive or ingenious. In the legal world, the word has implications for patent rights. There is no evidence that Einthoven had strong aspirations for a controlling patent. Snellen[5] mentioned that any such claims would be abrogated by the publication in 1909 of the detailed specifications of his string galvanometer. I believe that within observed patent practices Einthoven's string galvanometer could have been patented because it was designed for a purpose and was a success in obtaining objectives not previously achieved. It was not a discovery and much more than a gadget, and I submit would meet one encyclopaedic definition of an invention.[6] Einthoven (1903) condensed his views of his accomplishments in these words. "I have constructed an apparatus . . . specifically designed to give direct registration of the human electrocardiogram which will give true readings."[7] Einthoven was generous in giving credit to other investigators. When he read a paper before the Chelsea Medical Society (1912) he praised Waller and Lewis, and credited Waller with coining the term electrocardiogram: "It gives me especial pleasure to bring to remembrance here that the human EKG was first recorded by a London physiologist, Augustus D Waller, who also introduced the term 'electrocardiogram' into science."[8] Einthoven was unhappy with the editing of this paper, as judged by his correspondence with Lewis.

Many scientists have apparently felt comfortable with the use of the word "invention" for the Einthoven instrument. Below is a list of short quotations from papers in which the word "invent" was used.

Waller (1909): "Professor Einthoven's results with . . . the extraordinarily sensitive galvanometer he has *invented* . . ."[9]

Lewis (1911): "The string galvanometer in its present form, the *invention* of Einthoven . . .".[10] In an obituary (1927) Lewis stated ". . . he moved to the principle of Ader's instrument . . . constructed a galvanometer greatly surpassing all previous instruments . . . created a piece of apparatus of unparalleled delicacy and accuracy."[11]

A V Hill (1927) (in obituary): "The problem of recording these small and fleeting changes . . . was solved in 1903 by the *invention* of the string galvanometer."[12]

H B Williams (1947): "Accordingly, I agree with you (A E Cohn) that the record should leave no doubts on the score that Einthoven was the *inventor* of the electrocardiograph."[13]

White (1949): "Finally in 1903 came the announcement of the *invention* of the accurate and practicable galvanometer (Einthoven)."[14] (Curiously in the first and second editions of *Heart Disease* the word used was "discovery"; this was changed to "invention" in the third edition.)

De Waart (1961): "Persevering in *inventing* and constructing his string galvanometer."[15]

Requests for reprints to Dr Howard B Burchell, 260 Woodlawn Avenue, St Paul, Minnesota, 55105, USA.

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Burch and DePasquale (1964): "(Einthoven) will always be remembered as the *inventor* of the string galvanometer."[16]

Zachary Cope (1973): "The great development of this subject was largely due to the *invention* of the string galvanometer by Einthoven."[17]

Snellen (1983): "The mathematical correction (of the capillary electrometer tracings) although satisfactory was cumbersome and Einthoven therefore *invented* a new instrument."[18]

The following are excerpts from work by other knowledgeable scientists. They are quoted because they use phrases or words that are equivalent to the word "invent":

Wenckebach (1927) (obituary): "Seine Grosstat, der er einen grossen Teil seines Lebens gewidmet, war das Saitengalvanometer."[19]

Samojloff (1930): "First of all, he is the creator of electrocardiography."[20]

Wilson (1940): (After work with capillary electrometer) "He was then able to determine the characteristics which an instrument suitable for his purpose (should have) and in 1903 he completed the first model of what has since been known as the string galvanometer."[21]

Barron (1950): "Realising the limitation of this method (capillary electrometer), he devised a more simple sensitive and accurate means of recording these fluctuating potentials."[22]

Wiggers (1961): "Einthoven, therefore, undertook careful mathematical studies of the characteristics of moving coil galvanometers which eventually led him to employ the principle that a wire placed between two magnets bows when traversed by an electric current."[23]

Adrian *et al* (1976): "Einthoven introduced the string galvanometer in 1901."[24]

The Nobel Committee, as is reflected by the presentation speech of Professor Johanssen,[25] avoided any controversy: the justification of the award was for Einthoven's "discovery of the mechanism of the electrocardiogram" (a somewhat ambiguous phrase), and Einthoven's name was "linked to the design of a physical instrument" (the string galvanometer). Einthoven's Nobel lecture was given in German, but there is an English translation in the published Nobel lectures. The title of Einthoven's address was "The string galvanometer and

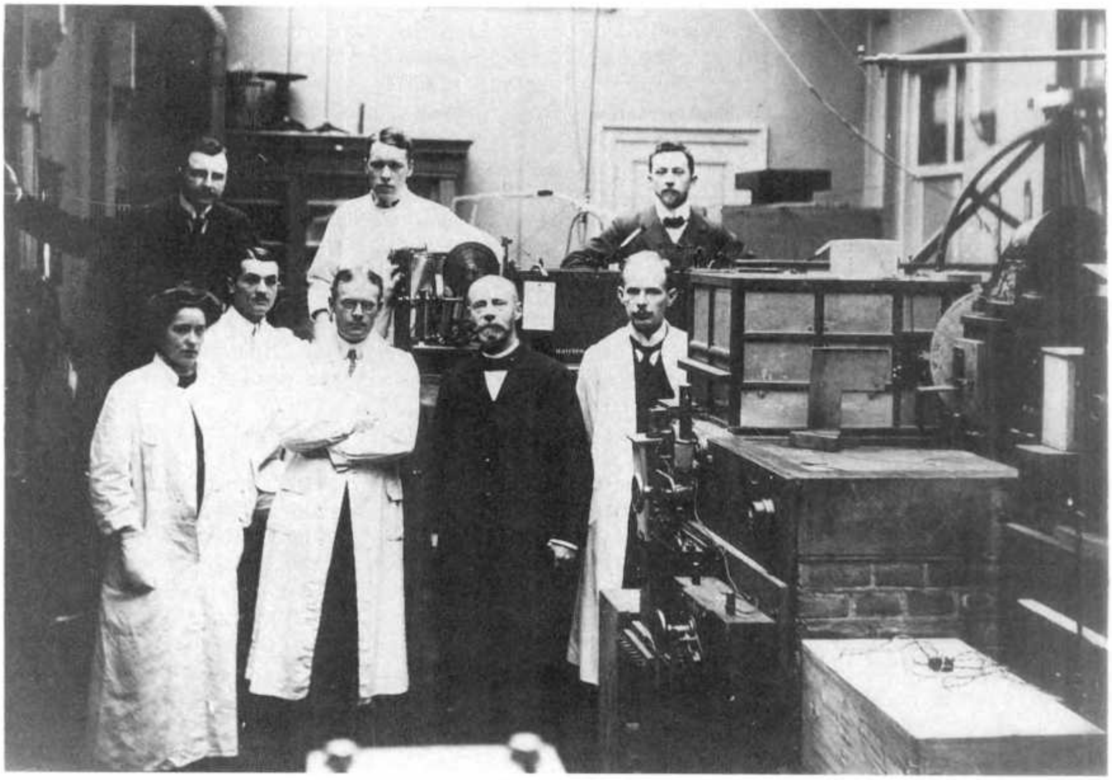

Figure *A photograph taken in Einthoven's laboratory in about 1908 given to the author by Dr George Fahr. The string galvanometer in the background is obscured. Dr Fahr is the young man on the left and Dr Einthoven is appropriately in the centre and at the front.*

the measurement of the action currents of the heart." This oration, as Snellen has pointed out, "constitutes an important review of a lifetime's work." All the 26 figures also reflect the high technical quality which he demanded in his records.

Those of us who have worked with a string galvanometer may be at a disadvantage when it comes to objectively assessing this instrument; love and admiration for the instrument may have engendered a bias. As well as saying that Einthoven "did not invent the string galvanometer" Cooper also states that "he was not the first to describe the electrocardiogram."[3] The claim that the PQRST wave form that was calculated by Einthoven from records taken on the capillary electrometer is the first true description of the electrocardiogram is not without support, as Professor Johanssen said in the Nobel presentation speech: "Einthoven can thus be named the discoverer of the real electrocardiogram." Einthoven added the U wave later in 1903. This was a contribution of the string galvanometer. Waller expressed his admiration for Einthoven's records, and mentioned specifically that with his own 1887 apparatus, "the P wave was not discernible."[9] Is it really correct to claim that Ader's galvanometer "was the type of instrument that Einthoven later used to introduce clinical electrocardiography": the implication being that Einthoven's instrument resembled that of Ader. It was many thousand times more sensitive, not merely an adaptation of the Ader instrument. Einthoven's credits to Ader in both his 1901 and 1909 papers[1 26] seem adequate to me. It is not reasonable to equate Einthoven's considerable improvements of the capillary electrometer with the profound changes that were needed to create his string galvanometer electrocardiograph from existing galvanometers. George Fahr, talking with me in his later years of his period with Einthoven, was candid in mentioning that Einthoven had rather clumsy hands and was somewhat secretive about his instrument when visitors came (this is contrary to the statements of others) (fig). Fahr, however, never said anything to impugn Einthoven's integrity or to imply that Einthoven had adapted Ader's instrument. In the late years (1920) there was some secrecy; access to the laboratory was forbidden on Fridays because of experimental wireless transmissions from Einthoven's son who was in the Dutch East Indies.

Burch and DePasquale recount a story, the source of which is not given, that Edelman manufactured the first galvanometers of the Einthoven design under an arrangement whereby Einthoven was to receive a $25 royalty for each instrument that was sold.[16] After adapting the instrument and using his knowledge of an existing Ader galvanometer Edelman reneged on payment of the royalty. Whatever the details of the falling out with Edelman, the event did initiate the development of companies in England[23] and the United States[13] to manufacture the string galvanometer with Einthoven's "blessing." Here then is prima facie evidence of a corporate acknowledgement of Einthoven's rights to a patent.

Einthoven would probably have approved Cooper's assertion that Bosscha "provided both a theoretical and practical support for Einthoven's work"; however, it still seems an exaggeration of Bosscha's role. He was not a teacher of Einthoven.

The labelling of the wave forms according to the PQRST convention was never explained in writing by Einthoven. Waller tried to maintain his original rubric "V_1 and "V_2" but he was unsuccessful in gaining disciples of his cause. I believe that Henson gives the best description of the origins of the PQRST nomenclature, which was based on the geometrical convention of Descartes (by coincidence in a book published in Leiden in 1637).[27]

My admiration of Willem Einthoven does not preclude a suspicion that he might have been possessive about "his" string galvanometer and that this attitude could have contributed to his estrangement from Edelman and the break up of his relationship with the clinicians in his hospital. Fahr relates[28] that the termination of the collaboration with the hospital physicians was engendered by an argument about who was to pay for the telephone line linking the hospital with the physiology laboratory for the transmission of electrocardiograms; another story was that "his occasional electrocardiographic arguments displeased the clinicians so much that in due course, the latter severed the connection." Wiggers[23] mentions in his encomium that Otto Frank once remarked "that in visit to Leiden, Einthoven had never invited him into his laboratory. It may be added parenthetically that Einthoven made a similar remark about Otto Frank."

Successful individuals rarely receive universal acclaim for being true gentlemen as did Einthoven. It is worth repeating a few sentences from the concluding paragraphs of his Nobel address:

> ". . . Thomas Lewis who has played a great part in the development of electrocardiography . . . I doubt that without his valuable contributions, I should have the privilege of standing before you today", . . . "in addition, innumerable other workers in the field of electrocardiography have gained great merit . . . investigators of the whole world have worked together . . . a new chapter has been opened in the study of heart diseases, not by the work of a single investigator, but by that of many talented men . . ."

Einthoven's "invention", the instrument that he bequeathed to us, endures. If one needed a high fidelity, high sensitivity galvanometer with nearly perfect square wave response over a remarkable frequency range (perhaps to celebrate a diamond jubilee of the beginnings of electrocardiography in American hospitals), one could confidently take an ancient string apparatus off the shelf and expect it to work superbly.

References

1 Einthoven W. Un nouveau galvanomètre. *Arch Neerl Sc Ex Nat* 1901;**6**:625–33.

2 Waller AD. A demonstration on man of electromotive changes accompanying the heart's beat. *J Physiol (Lond)* 1887;**8**:227–34.

3 Cooper JK. Electrocardiography 100 years ago: origins, pioneers, and contributors. *N Engl J Med* 1986;**315**:461–4.

4 Barker LF. Electrocardiography and phonocardiography. A collective review. *Bull Johns Hopkins Hosp* 1910;**21**:358–89.

5 Snellen HA. *Selected papers on electrocardiography of Willem Einthoven, with bibliography, biographical notes and comments.* Leiden: Leiden University Press, 1977:14.

6 Hall AR, Smith NAF. Invention. *Encyclopedia Americana.* New York: Americana Corporation, 1970; **15**:326–38.

7 Einthoven W. Die galvanometrische Registrirung des menschlichen Elektrocardiogramms, zugleich eine Beurteilung der Anwendung des Capillar-Elektrometers in der Physiologie. *Pflügers Arch* 1903;**99**:472–80.

8 Einthoven W. The different forms of the human electrocardiogram and their signification. *Lancet* 1912;**i**:853–61.

9 Waller AD. The electrocardiogram of man and dog as shown by Einthoven's string galvanometer. *Lancet* 1909;**i**:44–50.

10 Lewis T. *The mechanism of the heart beat.* London: Shaw and Sons, 1911:18.

11 Lewis T. Willem Einthoven [Obituary]. *Br Med J* 1927;**ii**:664–5.

12 Hill AV. Einthoven [Obituary]. *Nature* 1927;**120**:591.

13 Williams HB. (In paper by Cohn) Recollections concerning early electrocardiography in the United States. *Bull Hist Med* 1955;**29**:469–74.

14 White PD. *Heart disease.* 3rd ed. New York: Macmillan, 1949:173.

15 De Waart A. Einthoven commemoration. *Am Heart J* 1961;**61**:357–60.

16 Burch GE, DePasquale NP. *A history of electrocardiography.* Chicago: Year Book Medical Publishers, 1964.

17 Cope ZA. Auguste Desirė Waller (1856–1922). *Med Hist* 1973;**17**:380–6 (p 384).

18 Snellen HA. *Two pioneers of electrocardiography. The correspondence between Einthoven and Lewis 1908–1926.* Rotterdam: Donker Academic Publishers, 1983:11.

19 Wenckebach K. Willem Einthoven. *Dtsch Med Wschr* 1927;**53**:2176.

20 Samojloff A. Reminiscences of the late Professor Willem Einthoven. *Am Heart J* 1930;**5**:545–8.

21 Wilson FN. *The electric currents associated with the heart beat. Selected papers. 1940.* Ann Arbor: Edwards Brothers, 1954:1–10.

22 Barron SL. The development of the electrocardiogram in Great Britain. *Br Med J* 1950;**i**:720–5.

23 Wiggers CJ. Willem Einthoven (1860–1927). Some facets of his life and work. *Circ Res* 1961;**9**:225–34.

24 Adrian RH, Channell RC, Cohen T, Noble D. The Einthoven string galvanometer and the interpretation of the T wave of the electrocardiogram. *J Physiol (Lond)* 1976;**63**:67P–70P.

25 Johanssen JE. *Nobel lectures. Physiology or medicine. 1922–1941.* Amsterdam: Elsevier, 1965:89.

26 Einthoven W. Die Konstruktion des Saitengalvanometers. *Pflügers Arch Ges Physiol* 1909; **130**:287–321.

27 Henson JH. Descartes and the ECG lettering series. *J Hist Med Allied Sci* 1971;**26**:181–6.

28 Fahr G. *Einthoven. Ik wilde weten. George Fahr Festschrift. 80th birthday.* Minneapolis: Lancet, 1962.

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Case reports

Transient shock and myocardial impairment caused by phaeochromocytoma crisis

T R D SHAW, P RAFFERTY, G W TAIT

From the Department of Cardiology, Western General Hospital, Edinburgh

SUMMARY A patient admitted to hospital after injury to the abdomen was found to have transient hypertension which was followed by profound hypotension. ST elevation developed and extensive myocardial akinesia was seen at echocardiography, but coronary angiograms at this stage were normal. After treatment with intravenous fluids and dopamine he progressively recovered normal cardiac function. A partly necrotic catecholamine secreting tumour was later removed from the abdomen and it is likely that a kick to the abdomen had damaged the tumour and the consequent release of catecholamine had triggered a phaeochromocytoma crisis.

Phaeochromocytomas can produce hypotension as well as hypertension, particularly when there has been a sudden release of catecholamines.[1] In these circumstances the heart may show evidence of myocardial impairment, so-called catecholamine myocarditis. We describe a patient who developed these features after a kick to the abdomen.

Case report

A 41 year old man was admitted because of abdominal pain after an assault in which he had been kicked in the abdomen and chest. He had generalised abdominal tenderness and haematuria. The results of an urgent Gastrografin meal and intravenous urogram were normal, but ultrasound showed a mass adjacent to the head of the pancreas; this was interpreted as a retroperitoneal haematoma. His pulse was initially regular at 80 beats per minute and there were no abnormal cardiac signs. Blood pressure at admission was 190/110 mm Hg, rising at nine hours later to 240/160. He was given an intravenous dose of hydralazine and the blood pressure settled at 160/100 mm Hg. The chest *x* ray film and electrocardiogram were normal.

Forty eight hours after admission signs of low cardiac output developed, but the patient did not have breathlessness or chest pain. The jugular venous pressure was not visible. His pulse was 120 beats per minute and blood pressure was 100/60 mm Hg, falling one hour later to 60/unrecordable, with no pulsus paradoxus. There was a loud gallop rhythm. The electrocardiogram now showed considerable ST elevation (fig 1a). A cross sectional echocardiogram showed akinesia of all areas of the left ventricle except the basal segments. Plasma lactic dehydrogenase concentration reached 4644 U/l (normal 72–395 U/l). After administration of intravenous plasma protein derivative, saline, and dopamine his extremities became warm and his blood pressure rose to 150/90 mm Hg.

On the fourth day after admission the patient started to vomit and his blood pressure became unrecordable. He was cold, clammy, and sweating profusely. A chest *x* ray film showed slight pulmonary congestion. Dopamine infused at a higher rate than the previous infusion increased the blood pressure, which fluctuated between 180/70 and 65/unrecordable mm Hg, while heart rate varied between 80 and 130 beats per minute. Considerable ST elevation (5 mm) persisted without development of Q waves. To establish whether the heart showed evidence of traumatic damage the patient underwent cardiac catheterisation. Initial aortic and left ventricular pressures were 55/40 and 55/0–4 mm Hg. One and a half litres of plasma protein derivative and 500 ml of saline were infused intravenously over 20 minutes. The aortic and left ventricular pressures rose to 160/95 and 160/10–35 mm Hg. Right atrial

Requests for reprints to Dr T R D Shaw, Department of Cardiology, Western General Hospital, Crewe Road, Edinburgh EH4 2XU.

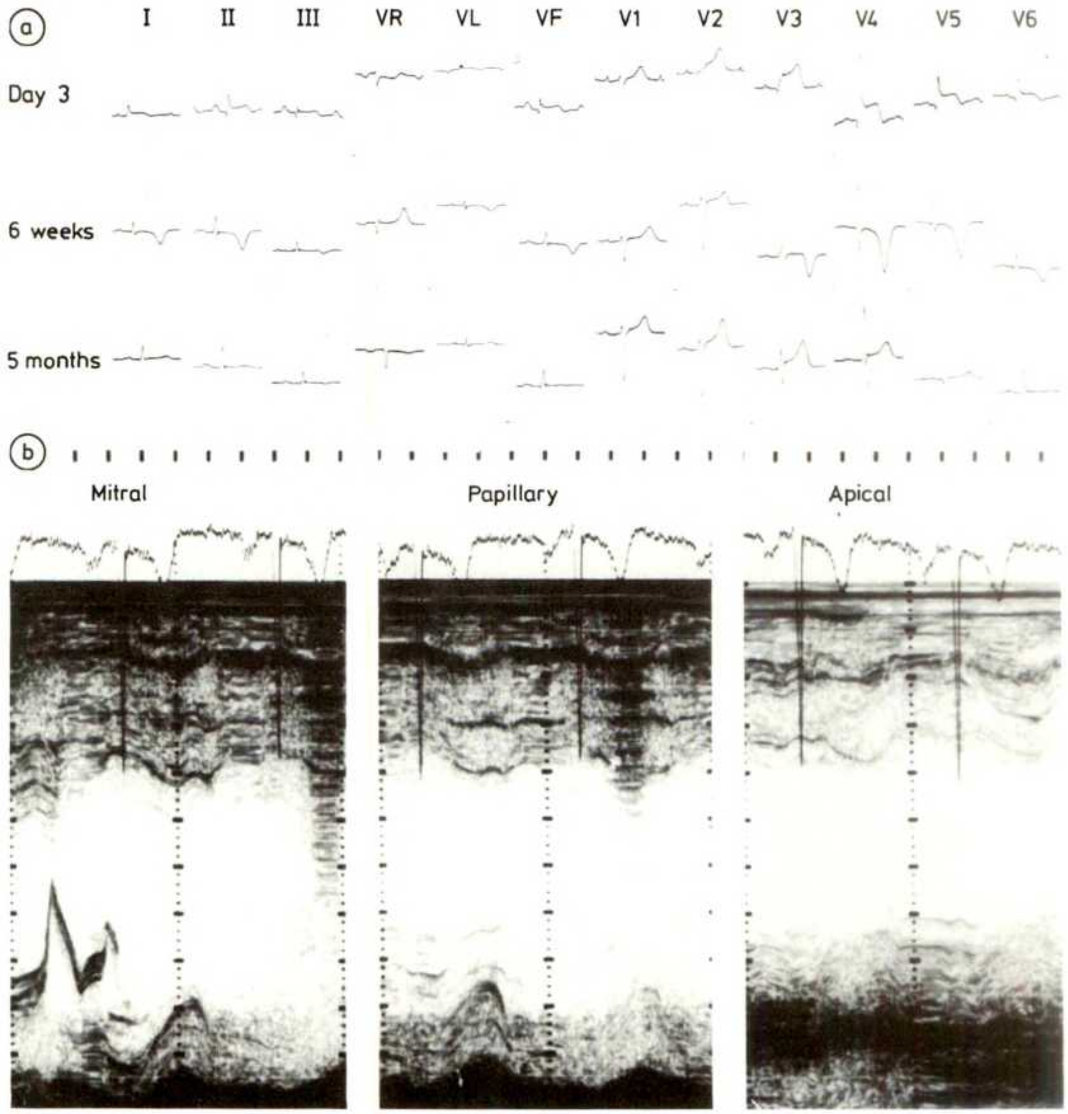

Fig 1 *(a) Electrocardiograms recorded three days, six weeks, and five months after admission. (b) M mode echocardiogram traces from mitral, papillary muscle, and apical levels of the left ventricle recorded five months after admission.*

pressure was then 15/7 and pulmonary artery pressure 63/35 mm Hg. A left ventricular angiogram showed hyperkinesis of the basal segments and the remaining areas of myocardium were akinetic (fig 2). The aortic root and the left and right coronary arteries, including their distal branches, appeared entirely normal (fig 2). Two litres of plasma protein derivative and one litre of saline were given overnight and pulse and blood pressure remained stable. Next day the patient showed transient confusion, agitation, and aggression but remained haemodynamically stable.

On day 6 after admission the patient was symptom free and had no abnormal abdominal signs. His pulse and blood pressure were normal. The electrocardiogram showed 1–2 mm ST elevation in the chest leads with T wave inversion in V2–V6. The echocardiogram now showed only mild hypokinesia. Ultrasound examination of the upper abdomen suggested slight reduction in the size of the retro-

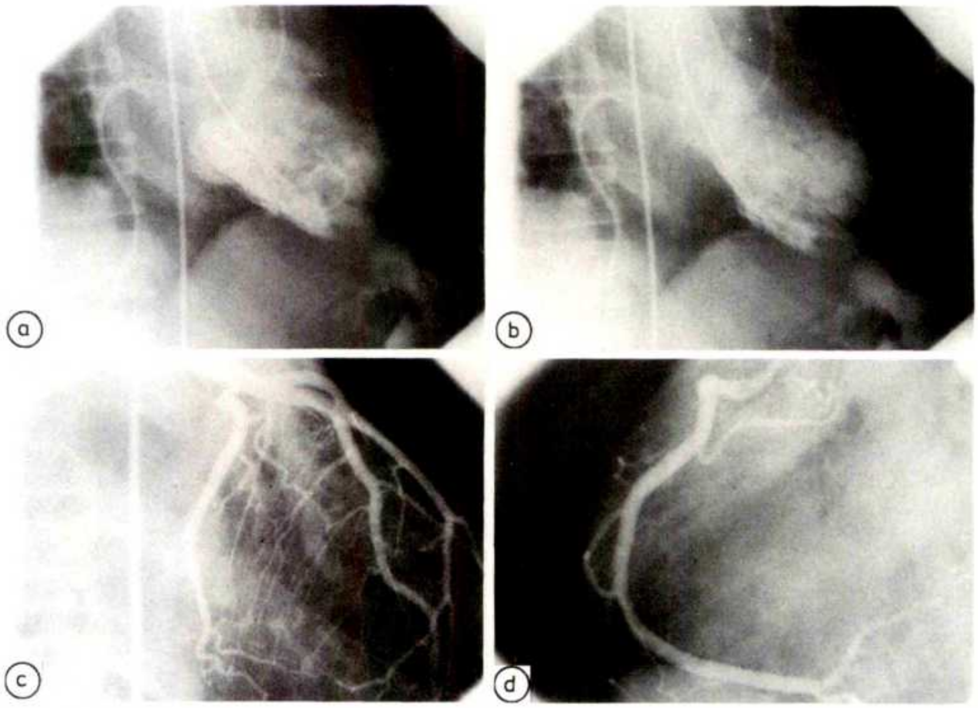

Fig 2 *(a) Left ventricular angiogram at end diastole (30° right anterior oblique view) (b) left ventricular angiogram at end systole, (c) left coronary angiogram, and (d) right coronary angiogram.*

peritoneal mass.

Over the next two weeks the patient continued to feel well. He was mobilised slowly because his electrocardiogram showed very deep (15 mm) symmetrical T wave inversion in the chest leads, but no arrhythmias had appeared at any stage and he remained normotensive.

At outpatient review six weeks after admission he was in sinus rhythm at 58 beats per minute and had a blood pressure of 122/78 mm Hg. There were no abnormal cardiac signs. An echocardiogram showed normal myocardial contraction but the electrocardiogram still showed deep T wave inversion (fig 1a). Ultrasound examination of the upper abdomen showed persistence of the retroperitoneal mass. Computed tomography of the abdomen showed a mass that lay anteromedial to the right kidney and inferior to the head of the pancreas. Both adrenal glands appeared normal. An ^{131}I-metaiodobenzyl guanidine isotope scan did not show any uptake at the site of the mass. Three 24 hour urine collections, however, showed an increase in urinary concentrations of conjugated metanephrines (5·6, 3·6, and 7·4 μmol/l; reference range 0–3 μmol/l). Three 24 hour urine collections for metanephrine estimation had been made during the first week of admission; however, conjugated metanephrines could not be measured in these collections because substances that interfered with the assay were present and could not be removed.

A 3 cm hard circumscribed mass was removed at operation. During operation the blood pressure rose to 230/130 mm Hg; this was controlled by intravenous labetolol. Transient agitation and aggression occurred two days after operation. The cut surface of the tumour was yellow with a necrotic centre and in formalin it turned dark brown. Light microscopy showed extensive central necrosis with peripheral areas of viable chromaffin cells. Electron microscopy confirmed the presence of membrane-bound secretory granules.

After operation the patient was physically well but he still had intermittent psychiatric symptoms. Urinary metanephrine concentration returned to normal. Five months after admission the T wave inversion of the electrocardiogram had disappeared (fig 1a). An echocardiogram confirmed a return to normal left ventricular contraction in all segments (fig 1b).

Discussion

This patient had a phaeochromocytoma crisis with a short hypertensive phase and a longer hypotensive phase. It may seem paradoxical that a low blood pressure can complicate a phaeochromocytoma but orthostatic hypotension is often seen in phaeochromocytoma patients who have hypertension when supine. Severe hypotension can be precipitated by induction of anaesthesia or by operation.[1] Blood volume is reduced in these cases and this is thought to be the result of a high sympathetic tone[2] or a state of autonomic dysfunction simulating ganglionic block.[3] A decrease in adrenocortical hormone has also been suggested as a factor.[4] Withdrawal of high catecholamine concentrations by removal of a phaeochromocytoma can also induce a severe hypotension which is associated with low intracardiac filling pressures.[1] Maintaining an adequate blood volume is therefore important in the perioperative management of phaeochromocytomas. Patients may also present in a hypotensive crisis.[5] Hypotension is an ominous sign when phaeochromocytoma is present. Van Vliet *et al* found that eight of 11 deaths followed a period of hypotension.[6] In our patient severe hypotension developed 48 hours after admission. It responded to large doses of intravenous fluids and dopamine.

The hypotension with phaeochromocytoma may be aggravated by myocardial impairment caused by high circulating catecholamine concentrations. The ability of adrenal extracts to create myocardial damage has been studied since the beginning of the century.[7] Van Vliet *et al* examined the myocardial structure in 26 necropsy cases with phaeochromocytoma.[6] Fifteen showed evidence of "active catecholamine myocarditis", the histological features of which were *(a)* focal degeneration and necrosis of myocardial fibres, *(b)* foci of inflammatory cells, *(c)* a diffuse oedema, and *(d)* an increase in fibrous tissue. Oedematous thickening of the small and medium sized arteries with partial fibrous replacement of the smooth muscle of the media was seen in a few of these cases. Most (24/26) showed left ventricular hypertrophy. Similar findings have been found in animals given noradrenaline or adrenaline and in patients receiving catecholamine treatment.[7] The clinical features of these abnormalities take various forms. In stable patients, cardiomegaly, electrocardiographic evidence of left ventricular hypertrophy, and T wave inversion are common.[6 8] Atrial and ventricular arrhythmias may occur. Phaeochromocytomas occasionally can be present in patients with normal blood pressure but with features of a chronic congestive cardiomyopathy that improves with removal of the tumour.[6 9 10] More dramatically, the patient may present with electrocardiographic evidence of ST elevation and deep symmetrical T wave inversion that resembles myocardial infarction.[6 8 9 11–15] The myocardium can subsequently return to normal[13] but aneurysm formation (with normal coronary arteries) has also been reported.[15] In our patient extensive left ventricular akinesia was shown by echocardiography and angiography for over 24 hours but normal contraction subsequently returned. The metabolic basis for such prolonged but temporary myocardial impairment is unclear. No coronary artery spasm was seen at this stage although ST segment elevation was present.

This patient's management was also complicated by acute psychiatric abnormality. An association between phaeochromocytoma and abnormal psychological states has been reported elsewhere.[16–18]

After recovery, our patient remained normotensive but had raised 24 hour urinary concentrations of metanephrine. A catecholamine secreting tumour with extensive necrosis was subsequently removed from the para-aortic area. Approximately 10% of phaeochromocytomas lie outside the adrenal glands.[1] The mass had initially been attributed to a retroperitoneal haematoma caused by the kicks to his abdomen. In three collections of urine for metanephrine assay during his first week of admission there was interference by unknown substances. Dopamine and other drugs had been given during that period. Stress and drugs can affect urinary metanephrine results and it is possible that necrosis of the tumour had released precursors and metabolites of catecholamines. An ^{131}I-metaiodobenzylguanidine scan has been useful for localising phaeochromocytomas but was negative in this case.[19]

External pressure, even from bending, can cause release of catecholamines from phaeochromocytoma[1] and severe necrosis or haemorrhage within a phaeochromocytoma has been shown to produce shock.[20–22] We believe that a kick to this patient's abdomen caused tumour necrosis and a massive release of catecholamines which led to his initial hypertension and the subsequent hypotension and myocardial impairment.

We thank Dr D B Horn and Dr J N Webb for their help.

References

1 Levine SN, McDonald JC. The evaluation and management of pheochromocytomas. *Adv Surg* 1984;17:281–313.

2 Brunjes S, Johns VJ Jr, Crane MG. Pheochromo-

cytoma: postoperative shock and blood volume. *N Engl J Med* 1960;**262**:393–6.

3 Engleman K. Phaeochromocytoma *Clin Endocrinol Metab* 1977;**6**:769–97.

4 Delarue NC, Morrow JD, Kerr JH, Colapinto RF Pheochromocytoma in the modern context. *Can J Surg* 1978;**21**:387–94.

5 McManus BM, Fleury TA, Roberts WC. Fatal catecholamine crisis in pheochromocytoma: curable cause of cardiac arrest. *Am Heart J* 1981;**102**:930–2.

6 Van Vliet PD, Burchell HB, Titus JL. Focal myocarditis associated with pheochromocytoma. *N Engl J Med* 1966;**274**:1102–8.

7 Hapt JI Cardiovascular injury induced by sympathetic catecholamines. *Prog Cardiovasc Dis* 1974;**17**:73–86.

8 Sutton MGStJ, Sheps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytoma: review of a 50-year autopsy series. *Mayo Clin Proc* 1981;**56**:354–60.

9 Baker G, Zeller NH, Weitzner S, Leach JK. Pheochromocytoma without hypertension presenting as cardiomyopathy. *Am Heart J* 1972;**83**:688–93.

10 Velasquez G, D'Souza VJ, Hackshaw BT, Glass TA, Formanek AG. Phaeochromocytoma and cardiomyopathy. *Br J Radiol* 1984;**57**:89–92.

11 Pelkonen R, Pitkanen E. Unusual electrocardiographic changes in pheochromocytoma. *Acta Med Scand* 1963;**173**:41–4.

12 Radtke WE, Kazmier FJ, Rutherford BD, Sheps SG. Cardiovascular complications of pheochromocytoma crisis. *Am J Cardiol* 1975;**35**:701–5.

13 Bouchez C, Ostermann G, Hecart J, Elaerts J, Bajolet A. Les manifestations cardiaques des pheochromocytomes. *Arch Mal Coeur* 1979;**72**:90–5.

14 Menozzi C, Monducci I, Vergoni W, Lolli G, Gheller G, Casali G. Infarto miocardico acuto in soggetti giovani quale manifestazione di feocromocitoma: a proposito di due casi. *G Ital Cardiol* 1982;**12**:604–8.

15 McGonigle P, Webb SW, Adgey AAJ. Phaeochromocytoma: an unusual cause of chest pain. *Br Med J* 1983;**286**:147–8.

16 Gillmer RE. Phaeochromocytoma—an interesting psychiatric presentation. *S Afr Med J* 1972;**46**: 174–6.

17 El Matri A, Slim R, Zmerli S, Ben Ayed H. Pheochromocytome avec troubles psychiatriques: un cas. *Nouv Presse Med* 1978;**7**:1467–70.

18 Bahemuka M. Phaeochromocytoma with schizophreniform psychosis. *Br J Psychiatry* 1983;**142**:422–3.

19 Valk TW, Frager MS, Gross MD, *et al.* Spectrum of pheochromocytoma in multiple endocrine neoplasia: a scintigraphic portrayal using ^{131}I-metaiodobenzylguanidine. *Ann Intern Med* 1981;**94**:762–7.

20 Huston JR, Stewart WRC. Hemorrhagic pheochromocytoma with shock and abdominal pain. *Am J Med* 1965;**39**:502–4.

21 Delaney JP, Paritzky AZ. Necrosis of a pheochromocytoma with shock. *N Engl J Med* 1969;**280**:1394–5.

22 Jones DJ, Durning P. Phaeochromocytoma presenting as an acute abdomen. *Br Med J* 1985;**291**:1267–8.

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Pulmonary regurgitation in transposition of the great arteries

SHAKEEL AHMED QURESHI,* JOSE A ETTEDGUI, OWEN D H JONES
From the Department of Paediatric Cardiology, Guy's Hospital, London

SUMMARY A female infant who presented with cyanosis and tachypnoea was found to have transposition of the great arteries, a ductus arteriosus, and a ventricular septal defect. An aortogram showed evidence of mild pulmonary regurgitation, which persisted after a Senning's operation; this is a hitherto unrecognised clinical finding.

Pulmonary regurgitation is not a recognised preoperative finding in transposition of the great arteries and it may not be of any importance when the definitive surgery entails venous redirection. When an arterial switch operation is contemplated, however, pulmonary regurgitation may become an important consideration because the pulmonary valve then functions as the aortic valve and its competence may be important in long term outcome.

This report shows that pulmonary valve regurgitation may be present in some patients from early infancy. This may influence the type of operation that is performed.

Case report

A female infant presented at the age of five weeks with increasing cyanosis and tachypnoea. There was a grade 2/6 pansystolic murmur at the lower left sternal edge and a continuous murmur at the second left intercostal space. The liver edge was palpable 2 cm below the right costal margin. The electrocardiogram showed sinus rhythm, right axis deviation, and right ventricular hypertrophy. The chest radiograph showed moderate cardiomegaly, pulmonary plethora, and a narrow vascular pedicle. The cross sectional echocardiogram was consistent with transposition of the great arteries with a ventricular septal defect.

CARDIAC CATHETERISATION

Table 1 shows data on haemodynamic function. Angiocardiography confirmed complete transposition of the great arteries, ventricular septal defect, and ductus arteriosus. An aortogram showed filling of the pulmonary artery via the ductus arteriosus. There was definite but mild pulmonary regurgitation. There was considerable clinical improvement after a balloon atrial septostomy.

When the patient was eight months old a Senning procedure was performed, the ventricular septal defect was closed with a Dacron patch, and the ductus was ligated.

Postoperatively she had a persistent grade 3/6 systolic murmur at the left sternal edge with residual cardiomegaly and pulmonary plethora on the chest radiograph. A first-pass radionuclide angiogram suggested a left to right shunt of 2·2:1

REPEAT CARDIAC CATHETERISATION

Table 2 shows data on haemodynamic function. Angiocardiography (left ventricle and aorta) showed no residual ventricular septal defect but there was a

Table 1 *Data on haemodynamic function before operation*

Site	*Pressure (mm Hg)*	*Saturation (%)*
SVC	—	28
IVC	—	43
MRA	Mean 3	37
RV	Systolic 90	—
	End diastolic 9	—
Aorta	90/40 (mean 60)	57
LA	Mean 6	96
LV	Systolic 90	87

SVC, superior vena cava; IVC, inferior vena cava; MRA, mid right atrium, RV, right ventricle, LA, left atrium; LV, left ventricle

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*Present address: Dr Shakeel A Qureshi, Department of Paediatric Cardiology, Royal Liverpool Children's Hospital, Myrtle Street, Liverpool.

Requests for reprints to Dr Shakeel Ahmed Qureshi, Department of Paediatric Cardiology, Royal Liverpool Children's Hospital, Myrtle Street, Liverpool L7 7DG.

Table 2 *Data on haemodynamic function after operation*

Site	*Pressure (mm Hg)*	*Saturation (%)*
SVC	Mean 8	49
IVC	Mean 7	55
SVA	Mean 7	58
LV	Systolic 45 End diastolic 7	58
PA	45/25 (mean 32)	88
PVA	Mean 10	98
RV	Systolic 80 End diastolic 10	98
Aorta	75/35 (mean 50)	98

See table 1 for abbreviations.
SVA, systemic venous atrium, PA, pulmonary artery; PVA, pulmonary venous atrium.

moderate sized ductus arteriosus through which an enlarged pulmonary artery became opacified. There was still some evidence of mild pulmonary regurgitation.

The ductus of 5 mm diameter was ligated through a left lateral thoracotomy and the child made a satisfactory recovery and is now symptom free.

Discussion

This patient initially had pulmonary regurgitation in the presence of severe pulmonary hypertension. Pulmonary regurgitation persisted after the Senning operation although pulmonary artery and left ventricular systolic pressures were greatly reduced. Because there was no discernible change in its severity, it is probable that the pulmonary regurgitation was caused by abnormal pulmonary valve structure. The abnormality must be a subtle one because neither the echocardiographic nor the angiographic appearances of the pulmonary valve were abnormal. Doppler ultrasonography was unhelpful in this case because the narrowness of the left ventricular outflow prevented correct positioning of the Doppler sample volume.

In the setting of venous redirection pulmonary regurgitation is of unknown but probably little haemodynamic importance. When an arterial switch is contemplated such incompetence of the valve, which is destined to support the systemic arterial pressures, may have a profound effect on the long term outcome.

Regurgitation of the aortic (previously pulmonary) valve has been reported in up to 20% of survivors after the arterial switch.[1–3] Castaneda *et al* reported trivial aortic regurgitation in 9% of the patients after a primary arterial switch in the neonatal period.[4] In another smaller series Quinones *et al* found trivial aortic regurgitation after operation in one out of nine patients who had undergone a primary arterial switch compared with four out of four patients who had had previous pulmonary artery banding.[5] This suggests that dilatation of the pulmonary artery proximal to the band is a possible explanation for the aortic regurgitation. Thus it appears that aortic regurgitation occurs less frequently after primary arterial switch in the neonatal period than after a two-stage switch. Nevertheless, it is still found in the neonatal group and this raises the possibility that it may have been present before operation. This finding is present despite the fact that the pulmonary valve in transposition of the great arteries has the gross appearance of a normal aortic valve with normal attachment to the subaortic curtain and the fibrous skeleton of the heart.[3] In patients undergoing more than one reinvestigation after operation, progression of aortic regurgitation has not been noted.[3 6 7]

The cause of the aortic regurgitation has been ascribed to the operative technique. The circumferential anastomosis close to the commissures has been incriminated together with, or as an alternative, the technique of coronary orifice reimplantation.[6] This implies that aortic regurgitation after the arterial switch is in theory preventable, but this case casts doubt on the possibility of prevention.

It is pertinent to ask whether pulmonary regurgitation can be diagnosed in transposition of the great arteries. In our case diagnosis by angiography was possible only because the pulmonary artery was opacified retrogradely via the ductus arteriosus. In the absence of a ductus pulmonary regurgitation cannot be demonstrated angiographically. The value of Doppler ultrasonography in this setting has not yet been defined. In some patients pulmonary regurgitation is difficult to assess because of the narrowness of the left ventricular outflow tract. Examination by additional colour Doppler, however, is an attractive possibility and this technique may help to show whether, in general, pulmonary regurgitation in transposition of the great arteries is present before, produced during, or appears after operation.

References

1 Yacoub MH, Bernhard A, Lange P, *et al.* Clinical and haemodynamic results of the two-stage anatomic correction of simple transposition of the great arteries. *Circulation* 1980;62:190–6.

2 Williams WG, Trusler GA, Freedom RM, Olley PM, Duncan WJ, Rowe RD. Results of arterial repair of transposition: the Toronto experience. *Pediatr Cardiol* 1983;4:99–104.

3 Yacoub MH, Kakichara R, Arensman FW, Radley-Smith R. Current status of arterial switch operation for the transposition of the great arteries. *Nippon Kyobu Geka Zasshi* 1983;31:623–33.

4 Castaneda AR, Norwood WI, Hougen T, Jonas RA, Mayer JE Jr. Primary anatomic repair of transposition of the great arteries with intact ventricular septum in the neonate. In: Doyle EF, Engle MA, Gersony WM, Rashkind WJ, Talner NS, eds. *Pediatric cardiology*. New York: Springer-Verlag, 1986:621–3.

5 Quinones JA, Duffy CE, Gidding SS, *et al.* Two-dimensional and Doppler echocardiographic assessment of anatomic correction for d-transposition of the great arteries. In: Doyle EF, Engle MA, Gersony WM, Rashkind WJ, Talner NS, eds. *Pediatric cardiology*. New York: Springer-Verlag, 1986:183–6.

6 Yacoub MH, Radley-Smith R. Venous versus arterial switch for the repair of transposition of the great arteries: a review. *Pediatr Cardiol* 1983;4:151–8.

7 Bernhard A, Yacoub MH, Regensburger D, *et al.* Further experience with the two-stage anatomic correction of simple transposition of the great arteries. *Thorac Cardiovasc Surg* 1981;29:138–42.

Br Heart J 1987;57:202–4

A rare variant of common arterial trunk

JEAN E RUBAY, FERGUS J MACARTNEY, ROBERT H ANDERSON*

*From the Thoracic Unit, The Hospital for Sick Children, London and *Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, London*

SUMMARY A 13 day old baby was admitted to hospital with multiple abnormalities, increasing cyanosis, and cardiac failure. Cardiac catheterisation was performed on the day of admission and he died shortly after the procedure. A rare variant of common arterial trunk, in which the pulmonary arteries arose directly from the underside of the aortic arch, was found at necropsy.

A common arterial trunk is defined as that condition in which a single arterial trunk leaves the heart through a single arterial valve and supplies the aorta, one or both pulmonary arteries, and the coronary arteries.[1] We have recently seen a case, unique to the best of our knowledge, in which the pulmonary arteries arose directly from the underside of the aortic arch. This variant is not accounted for in the classic categorisation of Collett and Edwards.[2]

Case report

CLINICAL FINDINGS

A 2·8 kg male baby was admitted to the intensive care unit at the age of 13 days because of increasing cyanosis and cardiac failure. The mother had been in contact with a rubella case at five months' gestation. After caesarean delivery the baby's Apgar scores were 7 and 9 at one and five minutes respectively. Multiple anomalies were noted, including a cleft lip, a short neck with webbing, a low posterior hairline, low set ears, and a very small penis. A systolic murmur was heard on examination of the cardiovascular system. He became cyanosed at the age of three days and went into cardiac failure during the first week. He was then transferred for more detailed cardiac investigations. Examination disclosed a cyanosed baby with an increased respiratory rate of 90 per minute, and a pulse rate of 150 beats/minute, femoral pulses that were variable in intensity, and an active heart with a loud ejection click with a grade (4/6) ejection systolic murmur best heard at the left sternal border. The second heart sound was single and the blood pressure was 80/50 mm Hg. The liver was palpable 3 cm below the costal margin.

Chest radiography showed mild cardiomegaly with increased pulmonary vascular markings. Cardiac catheterisation showed a large left to right shunt at the atrial level and a considerable increase in both ventricular end diastolic pressures. Angiocardiography revealed a common arterial trunk with ventricular septal defect and markedly impaired ventricular function. The pulmonary arteries were noted to originate from the underside of the aortic arch (fig 1a). The baby remained in a poor condition and after angiocardiography a severe progressive bradycardia developed. All attempts at resuscitation were unsuccessful.

At necropsy the heart showed the usual atrial arrangement (situs solitus). The right atrium received the inferior systemic return. The right superior caval vein was absent, the superior venous drainage returning through a left superior caval vein that drained through the coronary sinus. There was a secundum atrial septal defect. The four pulmonary veins were connected to the left atrium. A solitary trunk arose exclusively from the right ventricle (fig 2). There was a ventricular septal defect in a subarterial position with fibrous continuity between the arterial valve and both atrioventricular valves. The left atrium and left ventricle were small, but were connected by a normally positioned mitral valve. The solitary arterial trunk gave rise to both coronary arteries and, from its superior aspect, to the innominate, the left common carotid, and the left subclavian arteries. Both pulmonary arteries originated directly from the underside of the aortic arch (fig 1b). No other sources of pulmonary blood supply were present.

Requests for reprints to Professor Robert H Anderson, Department of Paediatrics, Cardiothoracic Institute, Brompton Hospital, Fulham Road, London SW3 6HP.

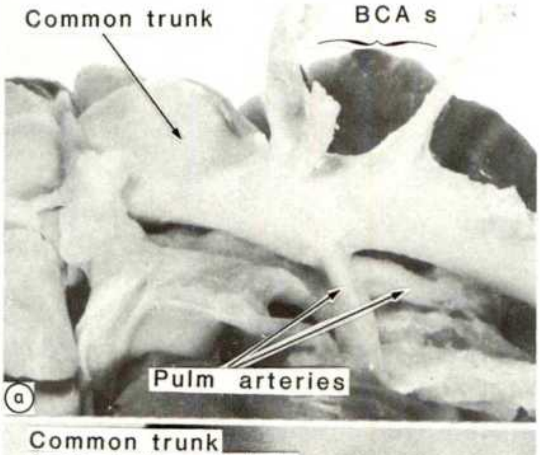

Fig 1 *(a) Photograph of the aortic arch at necropsy. Note that the pulmonary arteries originate from the underside of the aorta opposite a point between the left carotid and subclavian arteries. BCAs, brachiocephalic arteries. (b) Lateral projection of a selective left ventriculogram.*

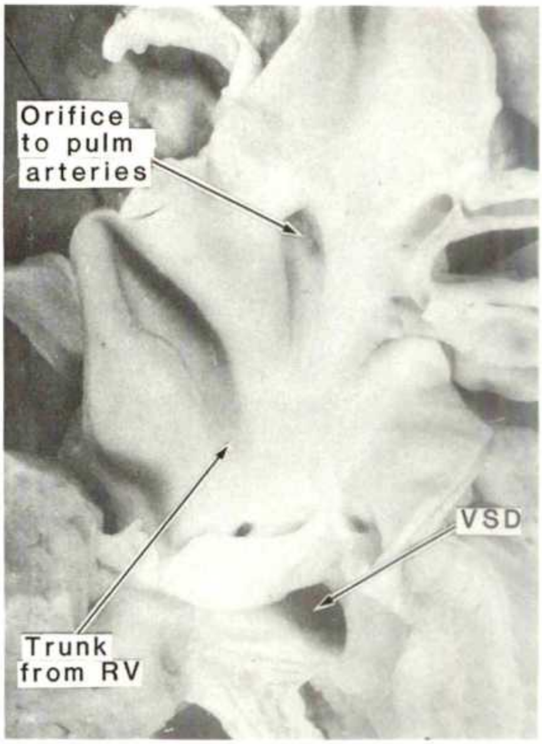

Fig 2 *Internal view of the ascending aorta and arch. Note the common origin of the pulmonary arteries.*

Discussion

The present case does not fit easily into conventional categorisations of common aortopulmonary trunk (truncus arteriosus communis). Though some would hold that a common arterial trunk can exist with two arterial valves,[3] we prefer to define this entity as a solitary arterial trunk guarded by a common arterial valve and directly supplying the coronary arteries, at least one pulmonary artery, and the systemic arteries.[1] Almost always the common trunk in this condition overrides the ventricular septum.

The first unusual feature of this case was the origin of the trunk entirely from the right ventricle. This rare variant has been well described.[1,4] The second distinctive feature was the site of origin of the pulmonary arteries. This feature was the basis of Collett and Edwards's well known classification.[2] According to these workers, in types I to III the pulmonary arteries arise from the ascending trunk, exhibiting a short common segment in type I, adjacent but separate origins in type II, and lateralised origins in type III. Their type IV is best described as a solitary arterial trunk, since in the absence of central pulmonary arteries (the intrapulmonary arteries being supplied by major collaterals) it is impossible to say whether the trunk is a common trunk or an aorta.[5]

The present case fits none of these categories. There are confluent central pulmonary arteries, but they arise from the arch between the left carotid and left subclavian arteries. They did not arise via an arterial duct, a persistent fifth aortic arch, nor from systemic/pulmonary collateral arteries. One might, with tongue in cheek, describe this case as "type III and a half", but in our view a better description would be "common arterial trunk with both pulmonary arteries originating from the arch of the aorta". We will not speculate upon the embryogenesis of this malformation. The case is to the best of our knowledge unique.

Dr Jean E Rubay was a visiting fellow from the Department of Cardiac Surgery, UCL, Cliniques Universitaires Saint-Luc, Brussels, Belgium. FJM is supported by the Vandervell Foundation; RHA by the Joseph Levy Foundation, and both are supported by the British Heart Foundation.

References

1 Crupi G, Macartney FJ, Anderson RH. Persistent truncus arteriosus. A study of 66 autopsy cases with special reference to definition and morphogenesis. *Am J Cardiol* 1977;**40**:569–78.

2 Collett RW, Edwards JE. Persistent truncus arteriosus: a classification according to anatomic types. *Surg Clin North Am* 1949;**29**:1245–70.

3 Van Praagh R, Van Praagh S. The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. *Am J Cardiol* 1965;**16**:406–25.

4 Thiene G, Bortolotti U, Gallucci V, Terribile V, Pellegrino PA. Anatomical study of truncus arteriosus communis with embryological and surgical considerations. *Br Heart J* 1976;**38**:1109–23.

5 Thiene G, Anderson RH. Pulmonary atresia with ventricular septal defect. Anatomy. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Paediatric cardiology 5*. Edinburgh: Churchill Livingstone, 1983:80–101.

Br Heart J 1987;57:205–6

Atrial fibrillation precipitated by tyramine containing foods

LEONARD H JACOB, D B CARRON

From the Grimsby District General Hospital, Grimsby, South Humberside

SUMMARY Episodes of atrial fibrillation that occurred after meals developed in a 60 year old man with a history of ischaemic heart disease. The attacks were precipitated by precursors and metabolites of tyramine and tyramine containing foods and drinks, in the absence of monoamine oxidase inhibitors. The patient has remained free of atrial fibrillation for the past twelve months on a diet that does not contain tyramine.

Case report

In 1980, at the age of 56 years, our patient was admitted to the hospital with central chest pain radiating to the left arm and in fast atrial fibrillation. Electrocardiography showed Q waves and ST segment elevation in the anterior chest leads V1–V5, and the plasma activity of the cardiac enzymes was increased, confirming the diagnosis of acute anterior myocardial infarction with atrial fibrillation. A few hours later acute left ventricular failure developed. He was treated with digoxin, diuretics, and anticoagulants. He quickly improved and recovered and sinus rhythm returned. He was transferred from the coronary care unit to the medical ward where he convalesced for 10 days and made a good recovery. Investigations—that is full blood count, urea and electrolyte concentration, liver function and thyroid function tests—were normal. He was discharged home in sinus rhythm on the above drugs.

He had a history of migraine in his twenties, which had been successfully treated by his general practitioner. There was no history of palpitation or heart disease nor of any psychiatric illness. He was married with three children and was a non-smoker. He drank two pints of beer a night and was not on any drugs. His father had died of heart disease at the age of seventy but there was no other relevant family history.

Two months later when he was reviewed in the outpatient clinic his condition was good, he was in sinus rhythm, and he was not in heart failure. He was maintained on digoxin and the other drugs were stopped. He was subsequently reviewed throughout 1981 at the clinic and his condition remained stable; he was eventually discharged back to the care of his general practitioner.

In February 1983 he was referred to the hospital after he developed attacks of palpitation and dyspnoea, and clinical examination disclosed atrial fibrillation and left ventricular failure, which were confirmed by electrocardiogram and chest *x* ray respectively. The dose of digoxin was increased to 250 μg/day and diuretics were started. He improved and was subsequently reviewed in the clinic and found to be in a stable condition and in sinus rhythm with a heart rate of 64 beats/min; the attacks of palpitation had become less frequent.

In May 1983 during one of his clinic reviews he mentioned for the first time that some of the attacks of palpitation occurred after meals. When he was questioned more closely about foods he suspected he identified cheese, chocolate, red wine, and bananas. Later after he had been asked to note his food more closely, he mentioned that broad beans and some tinned food with preservatives had also precipitated palpitation. Urinary concentrations of catecholamines and 5-hydroxyindolacetic acid were normal, however.

There was clearly some connection between the foods he mentioned and the palpitation which was not prevented by digoxin. A change to amiodarone improved control but did not abolish palpitation. He was advised to avoid foods containing tyramine, phenylalanine, and tyrosine. Two 24 hour Holter recordings obtained while he was on this diet showed sinus rhythm and no episodes of atrial fibrillation. Atrial fibrillation occurred when he was challenged with tyramine containing foods during 24 hour Hol-

Requests for reprints to Dr D B Carron, Grimsby District General Hospital, Scartho Road, Grimsby, South Humberside DN33 2BA.

ter recording; this coincided with the occurrence of palpitation. Palpitation occurred about one hour after the challenge, despite continuing amiodarone treatment, and resolved when sinus rhythm returned three to four hours after meals.

Urine collected during the test contained normal concentrations of catecholamines. A tyramine provocative test was planned, but a right sided transient ischaemic attack developed after a bout of palpitation brought on by his eating home baked bread made with dried yeast. This episode was considered to be embolic and he was started on anticoagulants. He later declined the provocation test.

Repeated outpatient reviews in 1985 showed that he remained in regular sinus rhythm without any attacks of palpitation. He was on amiodarone 200 mg per day and warfarin according to the British Comparative Ratio.

After he had been in sinus rhythm for more than six months he agreed to be challenged. Holter recording for 24 hours again disclosed a period of atrial fibrillation that coincided with reports of palpitation in the patient's symptoms diary and occurred after consumption of the specially prepared high tyramine test diet. Sinus rhythm returned within a few hours.

For the past 12 months he has taken a diet free of tyramine, its precursors, and metabolites, and has not had palpitation. He was last reviewed in the outpatient clinic in March 1986 when he was in sinus rhythm and in good health.

Discussion

Foods and drinks such as cheese, dried yeast, red wine (Chianti), yoghurt, pineapple, bananas, ice cream, and chocolate are known to produce hypertensive crises in patients on monoamine oxidase inhibitors. Phenylalanine, tyramine, serotinin, tyrosine, and noradrenaline are the vasoactive amines most commonly found in these foods.[1] Phenylalanine is metabolised to tyrosine, which is decarboxylated to tyramine and also to dopa, dopamine, and noradrenaline.[2] Tyramine increased noradrenaline in the coronary sinus blood in patients with ischaemic heart disease.[3] The increase in the heart rate-blood pressure product was not, however, found to be significant. Cardiac arrhythmias, such as sinus tachycardia, atrial ectopic impulses, ventricular ectopic impulses, and Wenckebach's phenomenon were induced in patients with pharmacologically untreated anxiety and depression when they were challenged with tyramine infusion[4] but to our knowledge atrial fibrillation has not been reported.

Although in our patient acute myocardial infarction was complicated initially by atrial fibillation, sinus rhythm returned while he was in hospital after the infarction and continued after discharge. Palpitation developed after consumption of tyramine containing foods and he was not on antidepressant drugs such as monoamine oxidase inhibitors. On two separate occasions tyramine challenge produced atrial fibrillation that was confirmed on 24 hour Holter recordings. We think that tyramine containing foods can precipitate cardiac arrhythmias, such as atrial fibrillation, in some patients with ischaemic heart disease.

We thank Miss A Priestley for the specialised dietetic advice.

References

1 Lovenberg DW. Psycho and vaso-active compounds in food substances. *J Agric Food Chem* 1974;22:23–6.

2 Martin DW, Mayes PA, Rodwell VW, Granner DK. *Harper's review of biochemistry*. 20th ed. California: Lang, 1985: 280, 305, 306, 327.

3 Forman MB, Robertson D, Goldberg M, *et al*. Effect of tyramine on myocardial catecholamine release in coronary heart disease. *Am J Cardiol* 1984;53:476–8P.

4 Tiller JWG, Dowling JT, Tung LH, Maguire KP, Rand MJ, Davies BM. Tyramine induced cardiac arrhythmias. *N Engl J Med* 1985;313:266–7.

Br Heart J 1987;57:207–9

Reversibility of primary pulmonary hypertension during six years of treatment with oral diazoxide

N S CHAN, J McLAY, A C F KENMURE

From the Department of Cardiology, Aberdeen Royal Infirmary, Aberdeen

SUMMARY A 32 year old woman presented with a syncopal attack and dyspnoea on exertion. A diagnosis of primary pulmonary hypertension was confirmed by clinical examination, cardiac catheterisation, and pulmonary angiography. Her symptoms resolved completely with oral diazoxide and the pulmonary arterial pressure was reduced to normal levels over a period of six years. When diazoxide was discontinued on two separate occasions pulmonary hypertension recurred. This demonstrated the continued presence of the underlying stimulus for vasoconstriction.

The prognosis in primary pulmonary hypertension is grave; the five year survival rate is <25%.[1] Although spontaneous remission has been reported, it is rare.[2 3] Though various agents including acetylcholine,[4] nifedipine,[5] tolazoline,[6] isoprenaline,[7] verapamil,[8] hydralazine,[9] and diazoxide[10] have been shown to lower pulmonary artery pressure when given by direct intra-pulmonary artery injection or sublingually, the results of long term oral treatment have been disappointing, with success being achieved in only a few patients.

We describe a patient with primary pulmonary hypertension in whom treatment with oral diazoxide caused a sustained reduction of pulmonary artery pressure accompanied by relief of symptoms. When treatment was discontinued on two separate occasions pulmonary hypertension recurred and the patient's symptoms returned. We hope that continued treatment with diazoxide will improve prognosis in this patient.

Case report

A 32 year old woman was admitted to Aberdeen Royal Infirmary in August 1979 after a syncopal episode. She had been in good health until 18 months before when she began to experience exertional dyspnoea and increasing fatigue. She also reported several episodes of central chest pain on exertion that were relieved by rest. At admission she was not taking oral contraceptive drugs and had never taken anorectic agents. She had had two uncomplicated pregnancies and her medical and family histories were unremarkable.

Physical examination showed that she was dyspnoeic at rest with moderate peripheral cyanosis. The jugular venous pressure was elevated at 7 cm with giant "a" waves. There was a prominent left parasternal heave with a palpable second sound at the pulmonary area. Auscultation revealed a wide physiological splitting of the second sound with a loud pulmonary component. Examination of the chest was normal.

Electrocardiography showed sinus rhythm with right axis deviation and a dominant R wave in lead V1 consistent with right ventricular hypertrophy. A radiograph of the chest demonstrated dilatation of the pulmonary trunk and main pulmonary arteries. An M mode echogram of the pulmonary valve showed loss of the "a" dip and conspicuous mid-systolic notching. There was also dilatation and hypertrophy of the right ventricle. Right heart catheterisation confirmed the presence of pulmonary hypertension with a pulmonary artery pressure of 90/40 mm Hg (mean pressure 66 mm Hg).

Pulmonary capillary wedge pressure was 7 mm Hg. Oxygen saturation studies showed no evidence of cardiac shunt. A pulmonary angiogram showed that the pulmonary trunk and main pulmonary arteries were considerably enlarged but that the peripheral vessels narrowed very rapidly. There was no evidence to suggest thromboembolic disease. Serological tests for antinuclear factor and lupus erythematosus cells were negative.

Requests for reprints to Dr A C F Kenmure, Department of Cardiology, Aberdeen Royal Infirmary, Aberdeen AB9 2ZB

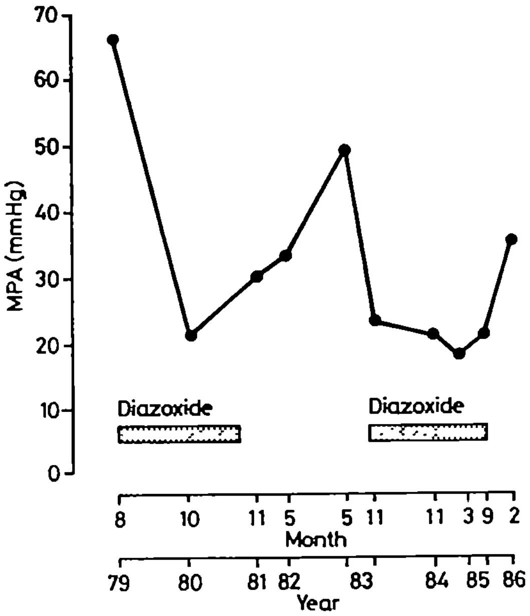

Figure *Changes over 6 ½ years in mean pulmonary arterial pressure (MPA) during diazoxide treatment and when treatment was withdrawn.*

TREATMENT AND PROGRESS

In view of favourable reports of the use of diazoxide in primary pulmonary hypertension,[10] the patient was treated with a dose of 150 mg daily which was gradually increased to 600 mg daily. At this dosage, however, postprandial nausea, facial oedema, and severe postural hypotension developed; the dose was reduced to 350 mg daily which gave a plasma concentration of 75 μg/ml (325 μmol/l).

She was discharged from hospital and was reviewed a month later. Although the findings on physical examination were unchanged, she reported improvement in her exercise tolerance, and her fatigue and chest pain had resolved completely. She had had no further syncope.

The electrocardiogram continued to show evidence of right ventricular hypertrophy but the total voltage of the R wave in V1 and the S wave in V6 was less than before.

Treatment was continued and in October 1980 she was admitted for repeat cardiac catheterisation. Her pulmonary artery pressure was now 27/14 mm Hg (mean 20 mm Hg). In view of this dramatic reduction in pulmonary artery pressure we initially thought that this must be a rare example of spontaneous regression and we gradually decreased the dose of diazoxide and stopped the drug completely in July 1981. Subsequent follow up, including serial measurements of pulmonary artery pressure, showed a gradual rise in pressure (figure) and this was accompanied by the return of her symptoms. Oral diazoxide (150 mg/day) was started again in July 1983 and again she responded favourably. Her pulmonary artery pressure remained within normal limits while she was on treatment and she was able to lead a normal active life with no major side effects.

In October 1985 a further attempt was made to withdraw treatment and diazoxide was discontinued. Repeat cardiac catheterisation in February 1986 again showed a further rise in pulmonary artery pressure (figure) and this was accompanied by a return of exertional dyspnoea. Treatment was started again at a dose of 150 mg a day and her symptoms disappeared.

Discussion

Diazoxide is a thiazide derivative which has a potent vasodilator effect on both the pulmonary and systemic arterial systems, but it is not a diuretic. The drug is thought to cause direct vasodilatation of the small pulmonary resistance vessels, reducing right ventricular afterload and thereby allowing a rise in cardiac output with corresponding relief of symptoms in primary pulmonary hypertension. Unfortunately a proportionately greater decrease in systemic vascular resistance may occur at the same time and this may be responsible for some of the reported dangers, including sudden death, of the use of vasodilators in this condition.[11 12] In our patient symptomatic postural hypotension developed when she was taking a high dose (600 mg/day), of diazoxide, but this disappeared when the dose was reduced to 350 mg a day. Initially she experienced nausea, fluid retention, and hirsutism; these ceased when the dose was reduced to 150 mg/day. Diabetes mellitus did not develop at any time.

Paul Wood first suggested that the initial event in primary pulmonary hypertension is sustained pulmonary arterial vasoconstriction of unknown cause that eventually results in the development of fixed obliterative vascular disease.[13] This view has been further supported by Wagenvoort and Wagenvoort[14] and Edwards and Edwards.[15] Such irreversible anatomical changes have been held to be responsible for the failure of vasodilator treatment but it has been postulated that such treatment might be effective if it were used before these permanent changes occur. The findings in our case support this concept and demonstrate that in some patients at least the vasoconstriction remains potentially reversible with long term treatment. This case also shows, however, that the stimulus to the development of pulmonary hypertension, whatever it may be, persists on withdrawal of treatment even after several years.

Spontaneous regression of the disease is rare.[2 3] Two cases have been reported; these patients were found to have had primary hypertension at the ages of 11 and 12 years. This had regressed by the time they reached early adult life; but most series show relentless progress of the condition[1] with most patients dying within five years of diagnosis. Long term oral treatment with vasodilators or other drugs, such as anticoagulants, has usually been disappointing except in a very small proportion of patients with primary pulmonary hypertension. A recent report demonstrated sustained improvement in primary pulmonary hypertension in a patient who was treated with sublingual isoproterenol for six years.[16] A sustained beneficial response to diazoxide was reported elsewhere,[10 17 18] but the maintenance of the efficacy of the drug over a six year period has not been shown before and raises the hope that early treatment may be effective in some cases. The patient might have responded beneficially to other agents with fewer side effects. Since her pulmonary hypertension was controlled with diazoxide at a dose less than that which caused side effects, however, we felt justified in continuing treatment with this drug.

References

1 Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984;**70**:580–7.

2 Bourdillon PDV, Oakley CM. Regression of primary pulmonary hypertension. *Br Heart J* 1976; **38**:264–70.

3 Fujii A, Rabinovitch M, Matthews EC. A case of spontaneous resolution of idiopathic pulmonary hypertension. *Br Heart J* 1981;**46**:574–7.

4 Samet P, Bernstein WH, Widrich J. Intracardiac infusion of acetylcholine in primary pulmonary hypertension. *Am Heart J* 1960;**60**:433–9.

5 Camerini F, Alberti E, Klugmann S, Salvi A. Primary pulmonary hypertension: effects of nifedipine. *Br Heart J* 1980;**44**:352–6.

6 Rudolph AM, Paul MH, Sommer LS, Nadas AS. Effects of tolazoline hydrochoride (Priscoline) on circulatory dynamics of patients with pulmonary hypertension. *Am Heart J* 1985;**55**:424–32.

7 Shettigar UR, Hultgren HN, Specter M, Martin R, Davies DH. Primary pulmonary hypertension: favourable effect of isoproterenol. *N Engl J Med* 1976;**295**:1414–5.

8 Malčić I, Richter D. Verapamil in primary pulmonary hypertension. *Br Heart J* 1985;**53**:345–7.

9 Packer M, Greenberg B, Massie B, Dash H. Hydralazine in pulmonary hypertension [Letter]. *N Engl J Med* 1982;**307**:1215–6.

10 Wang SWS, Pohl JEF, Rowlands DJ, Wade EG. Diazoxide in treatment of primary pulmonary hypertension. *Br Heart J* 1978;**40**:572–4.

11 Buch J, Wennevold A. Hazards of diazoxide in pulmonary hypertension. *Br Heart J* 1981;**46**.401–3.

12 Rubino JM, Schroeder JS, Wade EG, Rowlands DJ. Diazoxide in treatment of primary pulmonary hypertension [Letters]. *Br Heart J* 1979;**42**:362–3.

13 Wood P. Pulmonary hypertension with special reference to the vasoconstrictive factor. *Br Heart J* 1958;**20**:557–70.

14 Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension: a pathologic study of lung vessels in 156 clinically diagnosed cases. *Circulation* 1970; **42**:1163–84.

15 Edwards WD, Edwards JE. Clinical primary pulmonary hypertension. Three pathologic types. *Circulation* 1977;**56**:884–8.

16 Pietro DA, La Bresh KA, Shulman RM, Folland ED, Parisi AF, Sasahara AA. Sustained improvement in primary pulmonary hypertension during six years of treatment with sublingual isoproterenol. *N Engl J Med* 1984;**310**:1032–4.

17 Hall DR, Petch MC. Remission of primary pulmonary hypertension during treatment with diazoxide. *Br Med J* 1981;**282**:1118.

18 Klinke WP, Gilbert JAL. Diazoxide in primary pulmonary hypertension. *N Engl J Med* 1980;**302**:91–2.

Br Heart J 1987;57:210

Correspondence

Radiation in cardiology

Sir,

Since the publication of our editorial in the *British Heart Journal* (1986;55:421–2) proposed regulations on the protection of patients from radiation have been circulated to interested parties by the Department of Health and Social Security.[1] These proposals will enshrine the 1984 European Economic Community directive *Radiation Protection of Persons Undergoing Medical Examination or Treatment*[2] as British law. To achieve an ALARA (as low as reasonably achievable) dose to the patient now becomes not only desirable but also a legal requirement. All medical workers in radiation must be either qualified—that is radiologists or radiographers—or undergo a simple course of training in the essential elements of good radiological procedure as set out in a new guide to good practice.

The regulations are expected to become law by the end of this year and they have implications not only for cardiologists in training but also for those who are established in the specialty.

M J Raphael,
National Heart Hospital,
London.

N E Tomlinson
Department of Radiological Sciences,
Guy's Hospital Medical School,
London.

References

1 The Ionising Radiations (Protection of Persons Undergoing Medical Examination or Treatment) Regulations 1986. Draft statutory instruments 1986 health and safety AC1/I1–6.

2 Radiation protection of persons undergoing medical examination or treatment. EEC Directive 84/466/Euratom.

Notices

British Cardiac Society

The Annual General Meeting for 1987 will take place in Dundee on 8 and 9 April 1987, and the closing date for receipt of abstracts was 6 January 1987.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

Argentine Society of Cardiology

An International Congress "50th Anniversary of the Argentine Society of Cardiology" will be held in Buenos Aires on 11 to 16 October 1987. Further details from Secretaria, Azcuenaga 980/86, 1115 Buenos Aires, Argentina.

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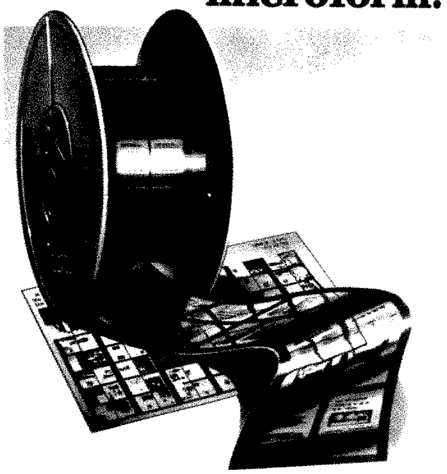

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MARJORIE GOTT HV RNT BA PhD,
MONICA HOWES BSc, Department of Health and Social Welfare, Open University, Milton Keynes

This book is the first serious attempt to meet the need for continuing education in heart disease risk reduction. It brings together key papers from a wide variety of international sources which demonstrate different ways of putting the principles of health education into practice, and teach the primary health care team how to tackle their preventive responsibilities with professional knowledge and skill. This book is the Course Reader for the Open University course 'Coronary Heart Disease: Reducing the Risk'; it is essential reading for all doctors and health care professionals.

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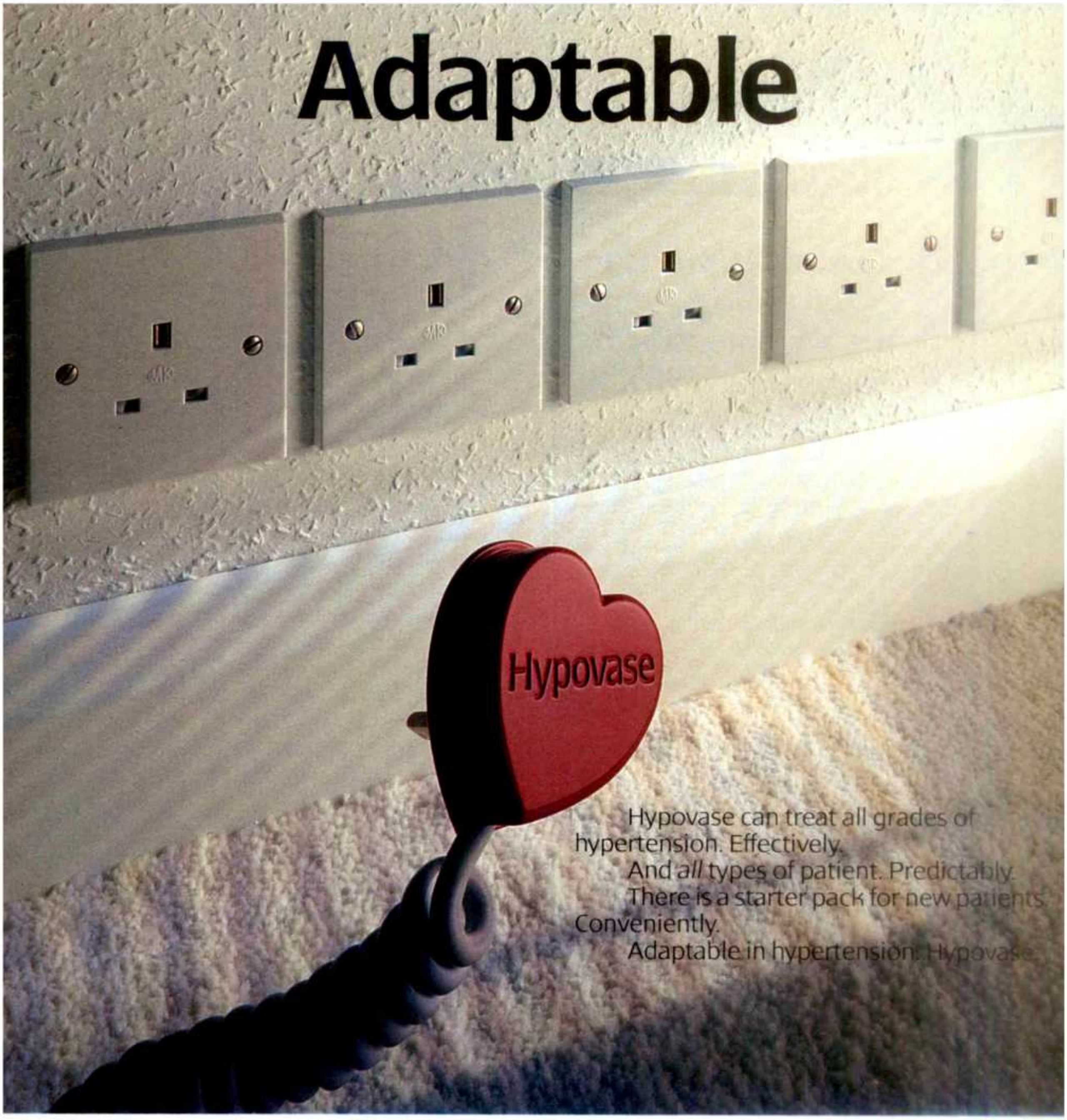

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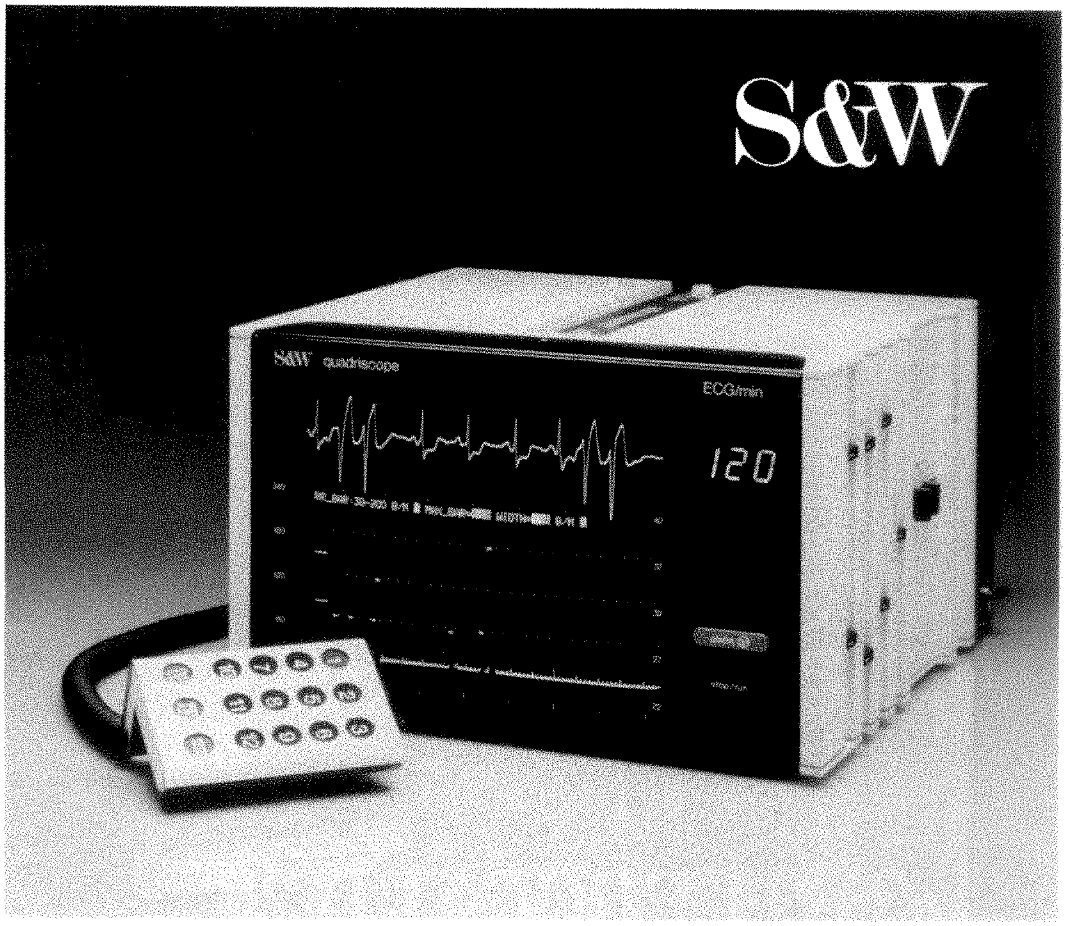

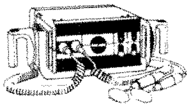
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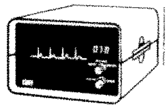
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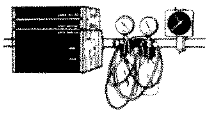
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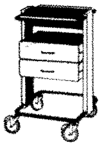
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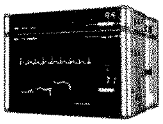
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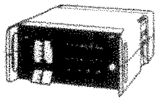
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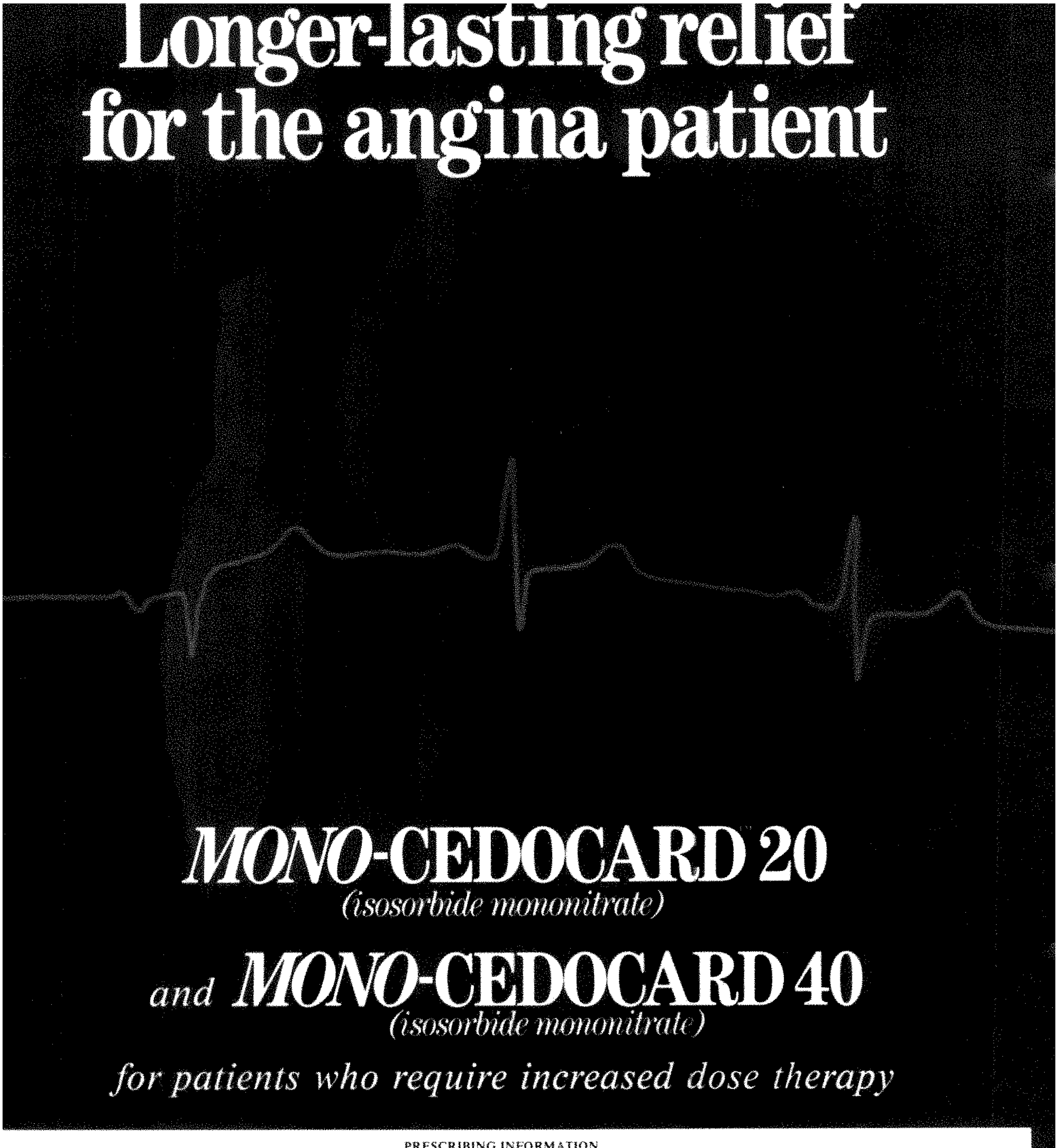

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Br Heart J 1987;57:211–3

Jubilee Editorial

Infective endocarditis 1937–1987

IAN R GRAY

From Walsgrave Hospital, Coventry

By 1937, infective endocarditis had long passed the milestones of pathological recognition, clinical identification, and bacteriological diagnosis. It was in the latter stages of being a progressively debilitating, incurably fatal disease that usually affected young people. Many of them were admitted repeatedly to hospital for treatment which was depressingly ineffective. I remember seeing such patients as a student and house physician, and how helpless one felt in the face of this unrelenting condition. Antibacterial treatment with sulphonamides was pointing the way towards eradicating infections of this kind but it rarely helped in endocarditis.

When penicillin became available towards the end of the second world war it was in very short supply. Indeed, in those early days, it used to be extracted from the urine of treated patients so that it could be re-administered. The dosage used was small by today's standards and treatment often had to be curtailed because supplies were so scarce. The earliest results of treating infective endocarditis were disappointing,[1] and it was not until 1944 that Loewe *et al* reported the recovery of seven patients given 200 000 units of penicillin daily with heparin.[2] As penicillin became more freely obtainable it was possible to treat large series of patients with infective endocarditis, and its efficacy was fully confirmed.[3] In infective endocarditis caused by streptococci of the viridans type an adequate dosage of penicillin given for a sufficiently long time nearly always eradicated the infection. Other streptococci, such as *Streptococcus faecalis,* were often much less sensitive; however, the discovery of the antibacterial synergy between penicillin and streptomycin[4] extended the range of antibiotic treatment. Later on, other derivatives of penicillin were synthesised which had properties that were useful in the treatment of infective endocarditis. Ampicillin and more particularly, amoxycillin are much better absorbed than benzyl penicillin or the phenoxypenicillins when given by mouth and they have a wider antibacterial spectrum. They were to make it possible to treat many patients with infective endocarditis with an oral antibiotic, so avoiding repeated injections or prolonged intravenous treatment.[5]

Some staphylococci are sensitive to penicillin and when such organisms caused infective endocarditis the disease could be treated in the same way as a streptococcal infection. Most strains, however, produce penicillinase, which renders them resistant to penicillin. Until semisynthetic penicillins resistant to penicillinase, such as methicillin, were developed such infections could seldom be overcome.[6]

Isoxazole penicillins, which combine resistance to penicillinase with resistance to gastric acid, made oral antistaphylococcal treatment possible. As the penicillins became more versatile, other antibiotics appeared that had comparable bactericidal properties. Vancomycin, clindamycin, fucidic acid, rifampicin, and the aminoglycosides all have a role in the treatment of certain patients with infective endocarditis; but none of them has displaced penicillin as the antibiotic of first choice.

The advent of penicillin and the antibiotic revolution which followed made it possible to eradicate the infection in nearly all cases of infective endocarditis, provided the diagnosis was made and treatment initiated sufficiently early. This unquestionably was the most dramatic change in infective endocarditis in the past 50 years. Deaths from infective endocarditis in England and Wales fell from 1200 per annum in the 1930s, when the disease was invariably fatal, to about 300 in 1950. In the 1980s there are still between 200 and 300 deaths each year (Registrar General's Statistics, personal communication). If one assumes a case mortality of 20 per cent there must still be an annual incidence of more than 1000 (more than 20 cases per million population). The incidence of infective endocarditis is about the same as it was in pre-antibiotic times.

The disease itself has changed in several ways. One outstanding difference is in the age of patients in whom infective endocarditis occurs. In the 1930s

Requests for reprints to Dr Ian R Gray, Walsgrave Hospital, Clifford Bridge Road, Walsgrave, Coventry CV2 2DX.

nearly two thirds of them were less than 40 years old. The age of patients has risen steadily so that infective endocarditis is now a disease of the middle aged and elderly.[7] The main reason for this is the decline in rheumatic fever—nowadays few young people have rheumatic valve lesions, which are vulnerable to infection. The routine closure of patent ductus has also subtracted a considerable number of young people from those at risk. Improved standards of dental hygiene in children may well have lessened the risk of infection from this source. At the same time, the longer survival of an earlier generation of those with rheumatic heart disease, some of whom have undergone valve replacement, provides an aging population that is susceptible to infection.

Whereas there are fewer infections of "rheumatic" mitral valves in young people, we now recognise that mitral valve prolapse is an important predisposing condition; and in older subjects degenerative changes in the mitral and aortic valves often seem to be important sites of infection. We have also come to realise that in many patients with infective endocarditis an affected valve was previously normal. A large and increasing number of patients have undergone valve replacement. Prosthetic valves have proved to be more vulnerable to infective endocarditis than the natural valves they replace. When prosthetic valve endocarditis occurs shortly after the operation it is usually a staphylococcal infection and mortality rates are high. An infection which occurs more than two months after operation (late prosthetic valve endocarditis) tends to be caused by the same organisms that infect natural valves.[8] Such infection can usually be controlled, but there is the risk, peculiar to mechanical valves, of the prosthesis becoming obstructed and immobilised by vegetations. Cardiac surgery is not the only intervention that can be responsible for extraneous infection of a heart valve. Infection may follow haemodialysis for renal failure; it can happen after pacemaker implantation and in patients on prolonged intravenous medication. Infective endocarditis also affects drug addicts who use contaminated needles and syringes for intravenous injections.[9]

Despite the various kinds of extraneous infection which have appeared in recent years, and which tend to be staphylococcal, there has been surprisingly little change in the spectrum of bacteria that cause infective endocarditis. Streptococci, mainly of the viridans type, continue to be responsible for between 60 and 70 per cent of infections, with staphylococci causing 20 to 30 per cent. *Staphylococcus epidermidis* has emerged as an important cause of infective endocarditis, particularly in prosthetic valve infections; *Coxiella burnetii* endocarditis is now well recognised, and fungal infection, usually with *Candida*, is a rare but serious problem.

The first intimation that surgery might have a part to play in the treatment of infective endocarditis was in 1940 when Touroff and Vessell reported the recovery of a patient with infective endocarditis after ligation of an infected ductus.[10] The major indications for surgery could not be realised, however, until valve replacement became possible. Before antibiotics were available most patients with infective endocarditis died of uncontrolled infection. A review of deaths from infective endocarditis in the 1950s revealed that by then cardiac failure had become the principal cause of death.[11] Cardiac failure in infective endocarditis is often caused by damage to valve structures by the infective process. There can be perforation of a valve cusp, detachment of an aortic cusp from the wall of the aorta, or rupture of chordae of the mitral valve. These lead to acute valve regurgitation which can cause a devastating volume overload of a small non-compliant recipient chamber with the rapid onset of severe left heart failure.

When valve replacement began to be widely practised in the early 1960s, acute valve rupture in infective endocarditis was perceived to be an important indication. Because of the dangers of carrying out major cardiac surgery in an infected field, valve replacement was at first postponed until antibiotic treatment had been completed. It soon became apparent, however, that the benefits of correcting the acute valve lesion outweighed such potential dangers, and valve replacement was increasingly carried out before the infection was fully controlled.[12] The improvement that often followed the operation was more dramatic and immediate than was usually the case in valve replacement for longstanding mitral or aortic regurgitation, and after 20 years it can still be seen in retrospect to have been a lifesaving intervention. With the success of valve replacement in patients with acute valve regurgitation even while infection was still active, it was a short step to valve replacement for the treatment of antibiotic resistant infections, covering the procedure with the best available antimicrobial regimen. Valve replacement is also necessary when prosthetic valve endocarditis causes obstruction of a mechanical prosthesis and in some patients who have had a major systemic embolus; it is even considered in patients with evidence of extensive vegetations.

Echocardiography is useful in infective endocarditis. M mode echocardiography, and, more particularly, cross sectional echocardiography provide a means of identifying larger vegetations on the heart valves, and also can demonstrate, without recourse to invasive forms of investigation, serious valve damage requiring surgical treatment. Echocardiography has its limitations: failure to demonstrate vegetations does not exclude the diagnosis of infective endocarditis, and the presence of vegetations does not necessarily imply that the disease is still active. It can sometimes be difficult to distinguish vegetations from a thickened or calcified valve, and prosthetic valves are very difficult to investigate. The technique, however, plays an important part in assessing vegetations, in following the progress of the disease, and in assessing the need for surgical intervention.

At the same time as antibiotic treatment of infective endocarditis became possible, antibiotic prophylaxis covering dental and other interventions became widely recommended—recommended but not necessarily practised. The facts that the incidence of infective endocarditis has hardly changed and that unprotected dental procedures and poor dental hygiene are still responsible for many cases of infective endocarditis speak for themselves.[13] The introduction of adequate oral rather than intramuscular antibiotic cover should increase the proportion of protected dental procedures,[14] but unfortunately in many of those in whom infective endocarditis develops heart disease is not recognised before the procedure, and prophylaxis cannot be considered. It is possible, too, that in such a common condition as mitral valve prolapse, the risk of infection may be outweighed by the risk of penicillin prophylaxis. When adequate antibiotic prophylaxis is given infective endocarditis rarely occurs. There are still many unanswered questions as to who requires antibiotic prophylaxis and in what circumstances, and we still do not know the portal of entry of infection in most cases of infective endocarditis.

The continuing mortality from infective endocarditis remains both a challenge and a reproach.[15] It is a challenge because we now have the means of treating effectively the microbial infections responsible for most cases and of correcting the destructive effects of infection on the heart valves. Despite this, antibiotic treatment is sometimes inadequate or inappropriate, and the need for surgical intervention is often unrecognised. It is a reproach because many cases of infective endocarditis are still only recognised at necropsy, and in many others the diagnosis is made only after weeks of illness. Delay in diagnosis means that a patient is at risk of major systemic embolism, cardiac failure, or renal damage for longer than need be. To fail to make the diagnosis of infective endocarditis in its early stages in 1937 was unfortunate: in 1987 it could be a disaster.

References

1 Florey ME, Florey HW. General and local administration of penicillin *Lancet* 1943;**i**.387–97.

2 Loewe L, Rosenblatt P, Greene HJ, Russell M. Combined penicillin and heparin therapy of subacute bacterial endocarditis: report of seven consecutive successfully treated patients *JAMA* 1944,124 144–9

3 Christie RV Penicillin in subacute bacterial endocarditis. Report to the MRC. *Br Med J* 1948;**i**·1–4.

4 Hunter TH. Use of streptomycin in treatment of bacterial endocarditis. *Am J Med* 1947;**2** 436–42.

5 Gray IR. The choice of antibiotic for treating infective endocarditis. *Q J Med* 1975;**44**:449–58.

6 Rolinson GN, Stevens S, Batchelor FR, Wood JC, Chain EB. Bacterial studies on a new penicillin—BRL1241 *Lancet* 1960;**ii**.564–7.

7 Hayward GW. Infective endocarditis a changing disease. *Br Med J* 1973;**ii**:706–9, 764–6.

8 Slaughter L, Morris JE, Starr A Prosthetic valvular endocarditis. A 12 year review. *Circulation* 1973; 47:1319–26

9 Dreyer NP, Fields BN. Heroin—associated infective endocarditis. A report of 28 cases. *Ann Intern Med* 1973;**78**:699–702.

10 Touroff ASW, Vessell H Subacute streptococcus viridans endarteritis complicating patent ductus arteriosus. recovery following surgical treatment. *JAMA* 1940;**115**:1270–2.

11 Robinson MJ, Ruedy J. Sequelae of bacterial endocarditis. *Am J Med* 1962;**32**:922–8.

12 Yeh TJ, Hall DP, Ellison RG. Surgical treatment of aortic valve perforation due to bacterial endocarditis. a report of 6 cases. *Am Surg* 1964;**30**:766–9.

13 Bayliss R, Clarke C, Oakley C, Somerville W, Whitfield AGW. The teeth and infective endocarditis. *Br Heart J* 1983,**50**:506–12

14 Working Party of the British Society for Antimicrobial Chemotherapy. The antibiotic prophylaxis of infective endocarditis. *Lancet* 1982;**ii**:1323–6.

15 Goodwin JF. The challenge and the reproach of infective endocarditis. *Br Heart J* 1985,**54**·115–8.

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Editorial

Fish and coronary artery disease

T A B SANDERS

From the Department of Food and Nutritional Sciences, King's College London, University of London

Does fish consumption protect against coronary heart disease? If so what are the mechanisms for such protection and how much fish (and of what types) would need to be consumed?

Atherosclerosis is apparently rare among Eskimos on a traditional diet of seal, caribou, and fish but not among those on a western diet.[1] Necropsy data showed that atherosclerosis was less severe in Canadian Eskimos[2] than in white Canadians. From an analysis of hospital records Kromann and Green concluded that acute myocardial infarction was extremely rare amongst Eskimos from the West Coast of Greenland who still eat large amounts of seafood.[3] The reliability of the mortality statistics for Eskimos may be questioned owing to a high mortality rate from accidents (for example through falling into holes in the ice) and a low necropsy rate. Cardiovascular mortality rates in Japanese fishermen, however, are reported to be lower than in Japanese farmers.[4] Fish based diets provide more protein, less saturated fat, and a different type of polyunsaturated fat than the average western diet.

Sinclair subsisted for three months on food derived entirely from marine animals, notably seal.[5] This resulted in considerable changes in haemostatic variables and serum lipids, especially in the fatty acid composition of the cholesterol esters and phospholipids. The most pronounced change was the replacement of polyunsaturated fatty acids of the $\omega6$ series, notably linoleic and its derivative, arachidonic acid, by those of the $\omega3$ series, notably eicosapentaenoic acid (20:5 $\omega3$) and docosahexaenoic acid (22:6 $\omega3$). The latter are the major polyunsaturates in marine animals whereas linoleic acid (18: $\omega6$) and α linolenic acid (18:3 $\omega3$) are the major ones in plant food.[6] Eicosapentaenoic acid and docosahexaenoic acid can influence the metabolism of lipoproteins and eicosanoids (prostaglandins, thromboxanes, prostacyclins, and leukotrienes) in a way that might afford protection from coronary artery disease.

Dietary values

Before discussing the various studies that have investigated the effects of fish or fish oil consumption, it is necessary to relate these studies to the amounts of eicosapentaenoic acid and docosahexaenoic acid provided by these foodstuffs. The fat content of fish varies seasonally, geographically, and by species[6 7] and is dependent on the marine food chain. White fish (cod, coley, plaice, haddock) contain about 1% fat by weight and oily fish (trout, salmon, mackerel, herring, pilchard, and sardine) contain 5–25% fat, depending upon when they are caught. In oily fish between 10% and 15% of the dietary energy is saturated fat compared with 1–2% in white fish. On an isocaloric basis oily fish provide about two to three times as much eicosapentaenoic acid and docosahexaenoic acid as white fish; 100 g of oily fish provides about 200 kcal (837 kJ), 1 g of eicosapentaenoic acid and 0·5–2 g of docosahexaenoic acid depending upon species; 100 g of white fish provides 96 kcal (402 kJ), 0·2 g eicosapentaenoic acid, and 0 3 g docosahexaenoic acid. A fish oil concentrate called MaxEPA (Seven Seas Health Care) has been used in some studies; 10 g provides 1·8 g eicosapentaenoic acid, 1·2 g docosahexaenoic acid, and 60 mg cholesterol.

Influence of the Eskimo diet on plasma lipoproteins

Greenland Eskimos have moderately low concentrations of low density lipoprotein (LDL) choles-

Requests for reprints to Dr T A B Sanders, Department of Food and Nutritional Sciences, King's College London, University of London, Campden Hill Road, London W8 7AH.

terol, very low concentrations of low density lipoprotein (VLDL) triglycerides, and high concentrations of high density lipoprotein (HDL) cholesterol compared with Eskimos living on a western diet.[8] The consumption of an Eskimo diet,[5] mackerel[9] (200 g/day) but not salmon,[10] or fish oil supplements (20 g/day)[11 12] slightly increased HDL cholesterol concentrations. Similar intakes considerably reduced triglyceride concentrations in both normal[9-11] and hypertriglyceridaemic subjects[13-15] by reducing the synthesis of both triglyceride[15 16] and apoprotein B(apoB)[16] in VLDL. In vitro studies have shown that eicosapentaenoic acid and docosahexaenoic acid are reversible inhibitors of hepatic triglyceride synthesis.[17]

Total plasma cholesterol concentrations are reduced by fish consumption but most of the reduction occurs in the VLDL fraction. Very high intakes of fish oil (90–120 g/day) do lower the concentration of both LDL cholesterol and LDL apoB by decreasing the rate of LDL synthesis.[18] Such high intakes also prevent the rise in plasma cholesterol obtained with dietary cholesterol.[19] At lower intakes (15 g/day), however, there is a tendency for LDL cholesterol and LDL apoB concentration[20] to rise, particularly in patients with type V hyperlipoproteinaemia.[14] A likely explanation is that a moderate intake of fish oil decreases hepatic triglyceride synthesis so that smaller than normal VLDL particles are secreted. These small particles are known[21] to be more readily converted to LDL than the larger triglyceride rich ones. Thus on the one hand the reduction in VLDL synthesis by fish diets probably reduces the risk of atherosclerosis, whereas on the other the increase in LDL may be deleterious.

Antithrombotic and anti-inflammatory effects

Evidence is emerging that suggests that protection against atherosclerosis may be afforded by a mechanism that overrides the influence of plasma lipoproteins. For example, intimal hyperplasia of vein grafts in hypercholesterolaemic dogs was inhibited by feeding fish oil.[22] A recent study showed that the development of coronary atherosclerosis in hyperlipidaemic pigs could be prevented by supplementing their diet with cod-liver oil.[23] It was argued that protection was afforded by changes in eicosanoid metabolism. It has also been argued that dietary eicosapentaenoic acid and docosahexaenoic acid decrease the risk of arterial thrombosis and mitigate damage to the myocardium by reducing local inflammation and by maintaining collateral circulation.[24]

Cyclo-oxygenase metabolites of arachidonic acid (20:4 $\omega6$), which have opposing effects in different locations, are believed to regulate platelet behaviour at the site of injury: thromboxane A_2 produced by platelets causes platelet aggregation and vasoconstriction; prostacycline PGI_2 produced by the vascular endothelium counteracts the effects of thromboxane A_2. Coronary atherosclerosis decreases the capacity of the endothelium to produce prostacyclin so that the balance between thromboxane and prostacyclin is altered in a direction that increases the risk of coronary thrombosis.[25] This view is supported by the observation that aspirin, which inhibits cyclo-oxygenase, halves the risk of myocardial infarction in patients with unstable angina.[26] Arachidonic acid is also converted to other important metabolites by platelets and neutrophils via the lipoxygenase pathway, which is not inhibited by aspirin. These metabolites, particularly leukotriene B_4, are strongly chemotactic for leucocytes and may be responsible for the massive leucocyte migration into the myocardium that occurs in the vicinity of an experimental coronary occlusion. The ability of eicosapentaenoic acid to partially inhibit both cyclo-oxygenase and lipoxygenase pathways may explain why the infarct volume in dogs in which myocardial infarction was experimentally induced was lower in those treated with fish oil than in controls.[24]

Dietary eicosapentaenoic acid and docosahexaenoic acid displace arachidonic acid from membrane phospholipids.[11 27] They also decrease the conversion of linoleic acid to arachidonic acid.[28] This incorporation of eicosapentaenoic acid into the erythrocyte membrane is accompanied by a reduction in whole blood viscosity and an increase in erythrocyte deformability[29]—phenomena which are unrelated to eicosanoid production. In subjects given large amounts of fish or fish oil (usually in excess of 15 g/day), however, the capacity to produce thromboxane A_2[30-32] and leukotriene B_4[33] is also reduced, but the urinary excretion of prostacyclin PGI_2 metabolites is not decreased[32 34] except in patients with atherosclerosis.[32] Dietary eicosapentaenoic acid and docosahexaenoic acid decrease the formation of eicosanoids derived from arachidonic acid, probably by displacing arachidonic acid from precursor pools and by acting as competitive inhibitions of cyclo-oxgenase[35] and lipoxygenase.[36]

Eskimos are liable to profuse nosebleeds and have extended template bleeding times; low platelet counts are also common.[8] Reductions in platelet counts are occasionally seen with very high intakes of marine oil[5] or fish oil.[27] However, the regular consumption of oily fish (200 g/day) or fish oil supplements (20 g/day) prolongs template bleeding time after about three weeks of treatment without affecting the platelet count[11,12,37] or the activity of clotting factors. Although there are similarities between the effects of consumption of oily fish and those obtained with aspirin, the reductions of thromboxane A_2 production and platelet aggregation are modest compared with those brought about by small doses of aspirin. Furthermore, because aspirin potentiates the prolongation of bleeding time brought about by fish feeding[37] it seems likely that a different mechanism is responsible especially as the urinary excretion of total prostaglandin metabolites is not significantly lower in Eskimos than in Danes.[38]

Eicosanoids can be formed from eicosapentaenoic acid but they tend to be less active than those derived from arachidonic acid. For example, thromboxane A_3[39,40] and leukotriene B_5[33] are less active but prostacyclin PGI_3 is as active.[39,40] Thromboxane B_3,[32,41] PGI_3,[32,34,42] and leukotriene B_5[43] have been detected after consumption of massive amounts of fish (400–800 g mackerel/day) or large amounts of fish oil (20–50 g/day). These observations support the hypothesis[44] that eicosapentaenoic acid modulates the production of active eicosanoids.

Potential hazards of high fish consumption

Fish is a good source of selenium but is a poor source of vitamin E. Myocardial fibrosis occurred in domesticated animals fed on oily fish and in infants fed rancid cod-liver oil.[45] This was caused by lipid peroxides. Precautions, therefore, need to be taken to guard against the formation of lipid peroxides, particularly in fish oil supplements, and to ensure an adequate intake of vitamin E. Mackerel, herring, and salmon gadoleic (20:1 ω11) and cetoleic (22:1 ω11) acids caused a transient myocardial lipidosis when fed to experimental animals in large amounts.[46] There is no evidence that eating these fish causes lipidosis in man, however. The salt content of many preserved fish (pickled herrings, kippers) is high,[6] and this may have an undesirable effect on blood pressure. Pickled fish also contains high concentrations of tyramine and histamine and so should be avoided by patients treated with monoamine oxidase inhibitors. Excessive intakes of histamine in spoilt oily fish are believed to be the cause of scomboid toxicity.[47] Fish are very susceptible to industrial pollution and are occasionally affected by naturally occurring toxins derived from the marine food chain.

Conclusion

It is necessary to eat large amounts of oily fish (>200 g/day) or smaller amounts of fish oil (about 10 g MaxEPA/day) to affect plasma lipid concentrations and eicosanoid production. Generally, larger amounts of fish oil are needed to alter eicosanoid production than to lower plasma triglycerides. Consumption of α linolenic acid, which is found in vegetable oils,[6,48,49] does not have the same effects as dietary eicosapentaenoic acid and docosahexaenoic acid.[50] A high intake of eicosapentaenoic acid and docosahexaenoic acid seems a plausible explanation for the low incidence of coronary artery disease among the Eskimos. Their extreme dietary practices are interesting because they shed light on the mechanisms leading to coronary artery disease; but it does not follow that such diets should be advocated for the general population.

Fish oil supplements have yet to be shown of value in the treatment of hypercholesterolaemia but they can be used to treat hypertriglyceridaemia. Multivariate analysis of several epidemiological studies suggests that plasma triglyceride concentrations is not an independent risk factor for coronary artery disease. None the less, there are several triglyceride bearing lipoprotein particles—chylomicrons, VLDL, and intermediate density lipoproteins (IDL)— and elevated plasma triglycerides may represent an increase in any one of these particles. A raised concentration of plasma triglyceride caused by raised chylomicron concentration is not associated with an increased risk of atherosclerosis, whereas raised concentrations of plasma triglyceride associated with raised VLDL and IDL concentrations are, even when LDL concentrations are low. Several recent angiographic studies showed that high concentrations of plasma triglyceride associated with raised VLDL and IDL were predictive of coronary atherosclerosis. In addition, there is evidence that VLDLs are toxic to the vascular endothelium.[51] Hypertriglyceridaemia is often accompanied by reduced concentrations of HDL cholesterol and a tendency to hypercoagulability. Since amelioration of hypertriglyceridaemia can both raise HDL cholesterol and reduce the level of certain clotting factors it is a potentially beneficial endeavour. This line of reasoning must, however, be tempered by the knowledge that moderate doses of fish oil not only reduce VLDL triglycerides but may also increase LDL concentrations at the same time. The overall assessment of risk will depend upon the size of the respective changes. Large quantities of fish oil seem free from this disadvantage but have the drawback of being too unpalatable for long term consumption.

There are reasons from believing that fish oil might be of benefit to patients with thrombogenic disorders, but the necessary clinical trials have yet to be carried out. Fish oil does prolong bleeding time and the precise mechanism for this effect remains uncertain. It may well involve altered vascular reactivity rather than altered platelet behaviour, especially as a recent study showed that fish oil supplementation lowered blood pressure.[52] It should be borne in mind that fish oil may well potentiate the action of some drugs such as aspirin and β blockers.

Formerly, fish was an important part of the British diet. It had the advantage of being available throughout the year. For religious reasons, it was eaten on Fridays and other fish days and almost daily during Lent. Lord Trenchard in his review of consumption patterns concluded that the decrease in fish consumption is one of the major changes in the British diet this century.[53] Cod-liver oil supplements were also widely used up until the 1950s. Fish contains several nutrients and foreign compounds that are scarce in other foods. For example, relatively small quantities of fish in the diet can contribute greatly to the total intake of retinol, vitamin D, taurine, and selenium. Consequently, fish might be providing some other yet to be identified protective factor. Selenium is a possible candidate, especially as selenium supplements prolong template bleeding time[54] and low serum selenium concentrations are associated with increased risk of coronary heart disease.[55]

Kromhout *et al* recently claimed that eating fish once or twice weekly might reduce the risk of coronary heart disease.[56] In this prospective study a reduction in risk was found with an average daily intake of 30 g fish (two thirds white fish, one third oily), an amount that would provide far less eicosapentaenoic acid and docosahexaenoic acid than the minimum shown to influence either plasma lipid concentrations or eicosanoid production. This effect was independent of other known risk factors such as smoking, blood pressure, and plasma cholesterol concentration. The protective influence of fish consumption has been confirmed in one study in the United States[57] but not in studies in Hawai[58] or Norway[59] where fish was consumed more frequently. In most cases the habitual diet of the subjects was assessed by a single 24 hour dietary recall. The assumption that one single dietary measurement is representative of an individual's diet over the next twenty years is dubious especially as food consumption patterns are continually changing. The association between modest fish consumption and protection from coronary heart disease requires further confirmation and must be assessed in the light of total mortality statistics. It is also necessary to consider which foods were replaced by fish.

Despite these uncertainties it makes good sense to encourage people to eat more fish, but not fried or salted, in place of foods with a high content of saturated fat (such as cheese, meat products, and fatty meats). Such a change would also be in accord with the current dietary guidelines for the prevention of coronary heart disease.[60]

References

1 Sinclair HM. The diet of Canadian Indians and Eskimos. *Proc Nutr Soc* 1953;**12**:69–82.

2 Schaeffer O. Medical observations on Canadian Eskimos *Can Med Assoc J* 1959;**81**:386–93.

3 Kromann N, Green A. Epidemiological studies in the Upernavik District, Greenland *Acta Med Scand* 1980;**208**:401–6.

4 Hirai A, Hamazaki T, Terano T, *et al*. Eicosapentaenoic acid and platelet function in Japanese. *Lancet* 1980,**ii**:1132–3.

5 Sinclair HM. Advantages and disadvantages of an Eskimo diet In. Fumagalli R, Kritchevsky D, Peoletti R, eds *Drugs affecting lipid metabolism*. Amsterdam: Elsevier/North Holland Biomedical Press, 1980:363–70

6 Paul AA, Southgate DAT *McCane and Widdowson's The composition of foods* 4th ed (MRC Special Report No. 297.) London: HMSO, 1978.

7 Ackman RG. Fatty acid composition of fish oils. In Barlow SM, Stansby ME, eds. *Nutritional evaluation of long chain fatty acids in fish oils*. London Academic Press, 1982:25–88.

8 Bang HO, Dyerberg J. Lipid metabolism in Greenland Eskimos. In: Draper HH, ed *Advances in nutrition research* New York· Plenum Press, 1980;**3**.1–40

9 Von Lossonczy TO, Ruiter A, Bronsgeest-Schoute HC, *et al*. The effect of a fish diet on serum lipids in healthy human subjects. *Am J Clin Nutr* 1978;**31**:1340–6

10 Harris WS, Connor WE, McMurry MP The comparative reductions of the plasma lipids and lipoproteins by dietary polyunsaturated fats. salmon vs vegetable oil. *Metabolism* 1983;**32**:179–84.

11 Sanders TAB, Vickers M, Haines AP Effect on blood lipids and haemostasis of a supplement of cod-liver oil, rich in eicosapentaenic and docosahexaenoic acids, in healthy young men *Clin Sci* 1981;**61**:317–24.

12 Saynor R, Verel D, Gillot T. The long term effect of dietary supplementation with fish lipid concentrate on serum lipids, bleeding time, platelets and angina *Atherosclerosis* 1984;**50**:3–10.

13 Simons LA, Hickie JB, Balasubramaniam S. On the effects of dietary n-3 fatty acid (MaxEPA) on plasma lipids and lipoprotein in patients with hyperlipidaemia. *Atherosclerosis* 1985;**54**:75–88

14 Phillipson BE, Rothrock DW, Connor WE, Harris WS, Illingworth DR. Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia *N Engl J Med* 1985;**19**:1210–6.

15 Sanders TAB, Sullivan DR, Reeve J, Thompson GR.

Triglyceride-lowering effect of marine polyunsaturates in patients with hypertriglyceridemia. *Arteriosclerosis* 1985;**5**:459–65

16 Nestel PJ, Connor WR, Reardon MF, *et al.* Suppression by diets rich in fish oil of very low density lipoprotein production in man. *J Clin Invest* 1984;**74**:82–9

17 Wong S, Reardon M, Nestel P Reduced triglyceride formation from long-chain polyenoic fatty acids in rat hepatocytes. *Metabolism* 1985;**34**·900–5.

18 Illingworth DR, Harris WS, Connor WE Inhibition of low density lipoprotein synthesis by dietary omega-3 fatty acids in humans. *Arteriosclerosis* 1984;**4**.270–5.

19 Nestel PJ. Fish oil attenuate the cholesterol induced rise in lipoprotein cholesterol. *Am J Clin Nutr* 1986;**43**:752–7

20 Sullivan DR, Sanders TAB, Trayner IM, Thompson GR. Paradoxical elevation of LDL apoprotein B levels in hypertriglyceridaemic patients and normal subjects ingesting fish oil. *Astherosclerosis* 1986; **61**:129–34.

21 Packard CJ, Munro A, Lorimer AR, Gotto AM, Shepherd J. Metabolism of apolipoprotein B in large triglyceride-rich very low density lipoprotein of normal and hypertriglyceridemic subjects *J Clin Invest* 1984;**75**:2178–92.

22 Landymore RW, Kinley CE, Cooper JH, *et al.* Cod-liver oil in the prevention of intimal hyperplasia in autologous vein grafts used for arterial bypass. *J Thorac Cardiovasc Surg* 1985,**89**:351–7.

23 Weiner BH, Ockene IS, Levine PH, *et al.* Inhibition of atherosclerosis by cod-liver oil in a hyperlipidemic swine mode *N Engl J Med* 1986;**315**·841–6.

24 Culp BR, Lands WEM, Lucches BR, Pitt R, Romson J. The effect of dietary supplementation of fish oil on experimental myocardial infarction. *Prostaglandins* 1980;**20**:1021–31.

25 Moncada S, Vane JR. Arachidonic acid metabolites and the interactions between platelets and blood vessel walls *N Engl J Med* 1979;**300**:1142–7.

26 Cairns JA, Gent M, Singer J, *et al.* Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter-trial. *N Engl J Med* 1985;**313**.1369–75.

27 Goodnight SH, Harris WS, Connor WE The effects of dietary ω3 fatty acids on platelet composition and function in man: a prospective controlled study. *Blood* 1981,**58**:880–5.

28 Brenner RR, Peluffo RO. Inhibitory effect of docosa-4, 7, 10, 13, 16, 19-hexaenoic acid upon the oxidative desaturation of linoleic into *f*-linolenic acid and of α-linolenic acid into octadeca-6, 9, 12, 15,-tetraenoic acid. *Biochim Biophys Acta* 1967;**137**:184–6.

29 Terano T, Hirai A, Hamazaki T, *et al* Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. *Atherosclerosis* 1983;**46**:321–31.

30 Siess W, Scherer B, Bohlig B, *et al.* Platelet membrane fatty acids, platelet aggregation, and thromboxane formation during a mackerel diet. *Lancet* 1980;**i**:441–4.

31 Lorenz R, Spengler U, Fischer S, *et al.* Platelet function, thromboxane formation and blood pressure control during supplementation of the western diet with cod-liver oil. *Circulation* 1983;**67**:504–11.

32 Knapp HR, Reilly AG, Allesandrini P, Fitzgerald GA. In vivo indexes of platelet and vascular function during fish oil administration in patients with atherosclerosis. *N Engl J Med* 1986;**314**:937–42.

33 Lee TH, Hoover RL, Williams JD, *et al.* Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *N Engl J Med* 1985;**312**:1217–24

34 Von Schacky C, Fischer S, Weber PC. Long-term effects of dietary marine ω3 fatty acids upon plasma and cellular lipids platelet function and eicosanoid formation in humans *J Clin Invest* 1985;**76**:1629–31.

35 Lands WEM, LeTellier PR, Rome LH, Vanderhoek JY. Inhibition of prostaglandin biosynthesis. *Adv Biosci* 1972;**9**:15–28.

36 Corey EJ, Shih C, Cashman JR Docosahexaenoic acid is a strong inhibitor of prostaglandin but not leukotriene biosynthesis. *Proc Natl Acad Sci USA* 1983;**80**:3581–4

37 Thorngren M, Gustafson A. Effects of 11 week increase in dietary eicosapentaenoic acid on bleeding time, lipids and platelet aggregation *Lancet* 1983, **ii**·1190–3.

38 Zuccato E, Hornstra G, Dyerberg J. Long term marine diet in Eskimos is not associated with altered urinary excretion of total tetranor prostaglandin metabolites. *Prostaglandins* 1985;**30**:465–77.

39 Needleman P, Raz A, Minkes MS, Ferrendelli JA, Sprecher HA. Triene prostaglandins prostacyclin and thromboxane biosynthesis and unique biological properties. *Proc Natl Acad Sci USA* 1979;**76**:944–8.

40 Gryglewski RJ, Salmon JA, Ubatuba FB, Weatherby BC, Moncada S, Vane JR Effects of all cis-5, 8, 11, 14, 17-eicosapentaenoic acid and PGI$_3$ on platelet aggregation. *Prostaglandins* 1979;**18**:453–78.

41 Fischer S, Weber PC. Thromboxane A$_3$(TxA$_3$) is formed in human platelets after dietary eicosapentaenoic acid (C20·5ω3). *Biochem Biophys Res Commun* 1983,**116**:1091–9.

42 Fischer S, Weber PC. Prostaglandin I$_3$ is formed in man after dietary eicosapentaenoic acid. *Nature* 1984;**307**:165–8.

43 Prescott SM, Zimmerman GA, Morrison AR. The effect of a diet rich in fish oil on human neutrophils. identification of leukotriene B$_5$ as a metabolite. *Prostaglandins* 1984;**30**:209–27.

44 Dyerberg J, Bang HO, Stofferson E, Moncada S, Vane JR. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis. *Lancet* 1978;**i**:117–9.

45 McCollum EV. *A history of nutrition* Cambridge Massachusetts· Riverside Press, 1957.

46 FAO/WHO. *Dietary fats and oils in human nutrition a joint FAO/WHO report.* Rome: FAO, 1977

47 Committee on Food Protection, Food and Nutrition Board, National Research Council. *Naturally occurring toxicants in foods* Washington· National Academy of Sciences, 1973.

48 Weiner MA. Cholesterol in foods rich in omega-3 fatty acids. *N Engl J Med* 1986;**315**:833.

49 Simopoulos AP, Salem N. Purslane: a terrestial source of omega-3 fatty acids. *N Engl J Med* 1986;**315**:833.

50 Sanders TAB, Roshania F. The influence of different types of ω3 polyunsaturated fatty acids on blood lipids and platelet function in healthy volunteers. *Clin Sci* 1983;**64**:91–9.

51 Gianturco SH, Eskin SG, Navarro LT, Lahart CJ, Smith LC, Gotto AM. Abnormal effects of hypertriacylglycerolemic very low-density lipoproteins on 3-hydroxy-3-methylglutaryl-coA reductase activity and viability of cultured bovine aortic endothelial cells. *Biochim Biophys Acta* 1980;**618**:143–52.

52 Norris PG, Jones CJH, Weston MJ. Effect of dietary supplementation with fish oil on systolic blood pressure in mild essential hypertension. *Br Med J* 1986;**ii**:104–5.

53 Lord Trenchard. The inter-relationship of marketing and nutrition. In: Yudkin J, ed. *Diet of man: needs and wants*. London: Applied Science Publishers, 1978:225–42.

54 Schiavon R, Freeman GE, Guidi GC, Perona G, Zatti M, Kakkar VV. Selenium enhances prostacyclin production by cultured endothelial cells. possible explanation for increased bleeding time in volunteers taking selenium as a dietary supplement. *Thromb Res* 1984;**34**:389–96.

55 Sallonen JT, Alfihan G, Huttunen JK, Pikkarainea J, Puska P. Association between cardiovascular death and myocardial infarction and serum selenium in a matched pair longitudinal study. *Lancet* 1982;**ii**. 175–9.

56 Kromhout D, Bosschieter EB, Coulander CL. The inverse relation between fish consumption and 20-year mortality from coronary disease *N Engl J Med* 1985;**312**.1205–9.

57 Shekelle RB, Missell L, Oglesby P, *et al*. Fish consumption and mortality from cardiovascular disease. *N Engl J Med* 1985;**313**:820.

58 Vollset SE, Heuch I, Bjelke E Fish consumption and mortality from cardiovascular disease. *N Engl J Med* 1985;**313**:820–1.

59 Curb JD, Reed DM Fish consumption and mortality from cardiovascular disease. *N Engl J Med* 1985;**313**:821–2

60 DHSS. *Diet and cardiovascular disease. Report on health and social subjects No 28*. London: HMSO, 1984

Br Heart J 1987;57:220–5

Long term angiographic follow up, cardiac events, and survival in patients undergoing percutaneous transluminal coronary angioplasty

SJEF M P G ERNST, TACO A VAN DER FELTZ, EGBERT T BAL,
LEO VAN BOGERIJEN, EDUARD VAN DEN BERG, CARL A P L ASCOOP,
H W THIJS PLOKKER

From the Department of Cardiology, St Antonius Hospital, Utrecht/Nieuwegein, the Netherlands

SUMMARY The results of percutaneous transluminal coronary angioplasty were studied in 1352 consecutive patients. The angioplasty procedure was angiographically successful in 1163 (86%) patients and the success rate increased gradually with time. There were no significant differences in success rates in different vessels or indications. The success rate for repeat coronary angioplasty was 92%. In 85% of the patients the clinical course was uncomplicated. Myocardial infarction occurred in 3·6%, emergency coronary bypass grafting in 2·6%, elective bypass surgery in 4·6%, and there were 10 deaths (0·7%). There were 16 deaths (10 non-cardiac) during follow up in the 1163 patients in whom the first procedure was successful. Actuarial analysis showed that after a first angioplasty 77·9% remained free of symptoms and cardiac events for five years and that after a second angioplasty 76% did so. Angiographic follow up showed restenosis in 24% of patients but the overall clinical success rate was 86·2%. On the basis of the intention to treat the procedure was successful in 74·3% of all 1352 patients. Coronary artery bypass surgery was eventually performed in 11·6% of all patients.

The long term angiographic success rate of coronary angioplasty is higher than previously suggested.

We report the angiographic and long term clinical results in a large number of consecutive patients who were treated with percutaneous coronary angioplasty.

Patients and methods

PATIENTS

From April 1980 to October 1985, 1889 patients had coronary angioplasty at the St Antonius Hospital in Utrecht (which is now in Nieuwegein). We have included only those patients in whom follow up lasted at least six months—that is 1352 patients who had coronary angioplasty before 1 January 1985. Eighty per cent of the patients were men.

All the patients had angina pectoris that responded poorly to medical treatment. In all patients with stable angina signs of myocardial ischaemia were demonstrated by excercise electrocardiographic studies or exercise scintigraphy. Seventy two per cent of the patients had angina pectoris of Canadian Heart Class III or IV. In 4% of the patients the severity of angina could not be coded properly because of recent thrombolytic (streptokinase) treatment.

Coronary angioplasty was performed as an elective procedure in 896 (66%) patients and in 355 (26%) patients it was performed because of impending myocardial infarction, which was defined as pain at rest accompanied by electrocardiographic ST-T changes without signs of myocardial necrosis occurring less than one week before the angioplasty procedure. Seventy two (5%) patients had had streptokinase treatment because of an acute myocardial infarction more than twelve hours before coronary angioplasty and in 17 patients the angioplasty attempt took place immediately after thrombolytic treatment. In 12 patients with an acute

Requests for reprints to Dr H W Thijs Plokker, St Antonius Hospital, PO Box 2500, 3430 EM Nieuwegein, the Netherlands

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myocardial infarction the acutely occluded vessel was approached with the balloon catheter without previous thrombolytic treatment.

Six per cent (82 cases) of the patients had aortocoronary bypass grafts and 9% (113 cases) had previous percutaneous transluminal coronary angioplasty. Nineteen per cent (259 cases) had suffered a myocardial infarction in the area related to the stenosis that was treated by angioplasty, 11% (143 cases) had an infarction elsewhere, and 1% (16 cases) had suffered myocardial infarctions both in stenosis related and unrelated areas.

ANGIOGRAPHIC PROFILE

Seventy per cent of the patients had single vessel disease. Left ventricular function was normal in 55% of the patients. Complete revascularisation (successful dilatation of all stenoses >50%) was thought to be possible in 78% of the patients. The severity of the stenosis was assessed by the means of multiple (angulated) angiographic views. The luminal diameter of the vessel at the narrowest portion of the stenosis was expressed as the percentage of the luminal diameter of the adjacent (normal) diameter, measured from a 12 fold magnified projection of the cine film on which the vessel contours were outlined by hand and measured with mechanical callipers.

PROCEDURE

Transluminal coronary angioplasty was performed via the femoral artery in 97% of the patients. After the first 361 patients had been treated a steerable balloon catheter system was used exclusively. In patients with multiple vessel disease the site considered to be the primary cause of the symptoms was first attempted. Multiple vessel disease was defined as stenoses of >50% in more than one major epicardial vessel.

An attempt at angioplasty was considered to be a success if the stenosis was reduced by >20% of the luminal diameter without complications that lead to myocardial infarction, coronary bypass operation, or death.

MEDICATION

After the first 100 patients all patients were routinely treated with anticoagulants, which ideally were started before angioplasty, and with heparin, dextran, and aspirin during the procedure, and anticoagulants plus either aspirin or dipyridamole for at least six months after the procedure.

FOLLOW UP ANGIOGRAPHY

Follow up angiography was performed in 62% (723) of cases. All patients were encouraged to have a follow up angiographic examination six months after the angioplasty. Naturally the proportion of patients with symptoms in the angiographic follow up group was higher than it was in the initial group. A restenosis was defined as a loss of >50% of the initial gain.

STATISTICAL ANALYSIS

The significance of differences was assessed by χ^2 analysis. Event free actuarial curves were based on the absence of recurrence of angina pectoris, myocardial infarction, repeat angioplasty, coronary bypass grafting, and death. The significance of difference between actuarial curves were assessed by the log-rank or Mantel-Haenszel test.

Results

The angioplasty attempt was successful in 1163 (86%) patients. The success rate was 87% (1281/1480) for stenoses. There was a clear increase in success rate with time and after the introduction of the steerable angioplasty system. There were no significant differences in success rates in different vessels.

The success rates in patients with stable angina and with impending myocardial infarction were not significantly different. The success rate for a repeat angioplasty was 92%. The success rate in patients with an immediate coronary angioplasty at the time of an acute myocardial infarction was 92% (11/12), the success rate for patients with an acute myocardial infarction who had coronary angioplasty immediately after thrombolytic treatment was 100% (17/17), and the success rate in patients who had coronary angioplasty ≥12 hours after thrombolysis was 87·5% (63/72).

Table 1 shows the clinical course in all 1352 patients. In 85% it was uncomplicated. Myocardial infarction occurred in 3·6%, emergency coronary

Table 1 *Clinical course in 1352 patients*

Course	*No*	%	
Uneventful	1146	85	
MI·			
STT	20	1·5	3·6%
QRS	29	2·1	
Emergency CABG*	36	2·6	
Elective CABG	64	4·6	
Deaths	10	0·7	
Minor problems	48	3·5	

STT, myocardial infarction without QRS changes; QRS, myocardial infarction with new Q waves on the electrocardiogram, CABG, coronary artery bypass grafting.

Minor problems include successful redilatations after occlusion of the vessel without myocardial infarction, ST changes without an increase in serum enzyme activity, and arrhythmias

*One patient died

artery bypass grafting was done in 2·6% (one of these 36 patients died after operation), elective bypass surgery was performed in 4·6%, and there were 10 deaths (0·7%). Angioplasty of the proximal left anterior descending artery was attempted in all but two of the patients who died, and it appeared to be successful initially. Minor problems such as ST changes without signs of myocardial infarction or arrhythmias occurred in 3·5% of the patients.

CLINICAL FOLLOW UP

Sixteen of the 1163 patients in whom the initial angioplasty procedure was successful died during follow up. There were six proven or suspected cardiac deaths and 10 proven non-cardiac deaths. Coronary bypass surgery had to be performed because of recurrence or progression of coronary artery disease or both in 58 (5%) patients. A second angioplasty was attempted in 95 (8%) patients.

In 13% of patients coronary angioplasty was performed in another vessel segment because of progression of atherosclerotic disease. Acute myocardial infarction occurred in the area related to the angioplasty site in six (0·5%) patients and in a non-related area in five (0·4%) patients. One patient who had successful angioplasty after thrombolytic treatment eventually underwent heart transplantation because of persisting severe left ventricular failure. Table 2 shows the late events.

Figure 1 shows the actuarial event free curve for all 1163 patients in whom the first coronary angioplasty procedure was successful. Angina generally recurred in the first six months, after this there were only a few cases of recurrence, and after five years 77·9% of the patients were free of symptoms and events. The mean follow up was 23·8 months. Exclusion of patients with previous coronary artery surgery, in whom symptoms recurred more often,

Table 2 *Late events in 1163 patients in whom a first coronary angioplasty procedure was successful*

Event	*No*	%
Total late mortality:	16	1·4
Cardiac	6	0·5
Non-cardiac	10	0·9
ACBG	58	5
Re-PTCA	93	8
PTCA other segments	13	1
AMI	6	0·5
AMI (non-related area)	5	0·4
Heart transplantation	1	

ACBG, aortocoronary bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; AMI, acute myocardial infarction.

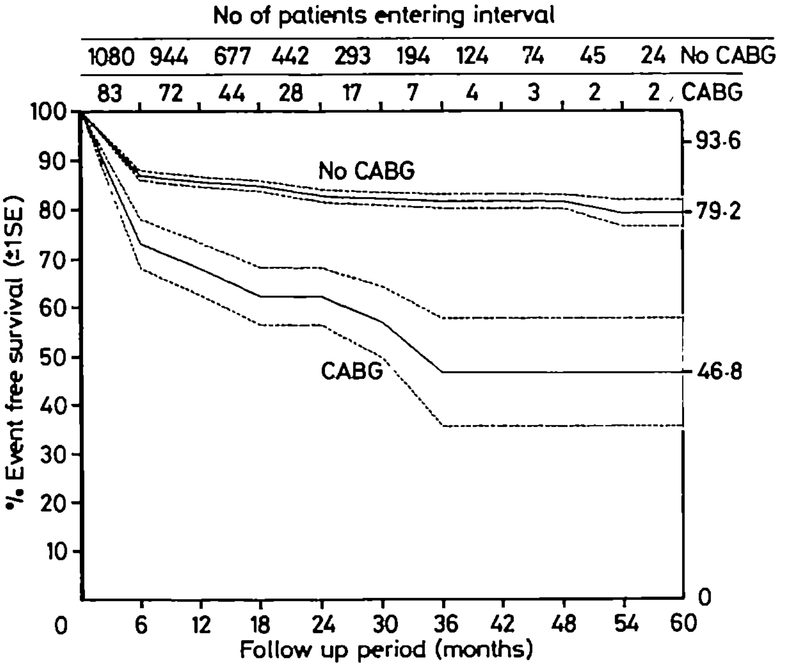

Fig 1 *Event free survival (actuarial) after successful coronary angioplasty in 1163 patients. No CABG, patients who had not previously undergone coronary bypass surgery. CABG, patients who had previously undergone coronary bypass surgery. Event free, no angina, myocardial infarction, death, redilatation, or bypass surgery. Broken lines indicate ± 1SE.*

produced a more level event free curve with 79·2% of the remaining patients being symptom free and having had no myocardial infarction, repeat coronary angioplasty, or coronary bypass grafting. Only 46·4% of the patients who had coronary bypass grafts were free of symptoms five years after angioplasty (p < 0·001 (fig 1)).

Patients who had coronary angioplasty because of stable angina pectoris and those with impending myocardial infarction had similar event free curves. After five years 78·6% of the patients with impending myocardial infarction at the time of successful coronary angioplasty are symptom free as are 74·5% of the patients with stable angina at the time of successful coronary angioplasty. Any symptoms associated with angiographic evidence of restenosis generally recur within six months (mean (SD) 4·8 (6·8)) of angioplasty. In the 40 patients without angiographic evidence of restenosis but with progression of the disease elsewhere symptoms recurred 17·6 (14·5) months after angioplasty.

The recurrence of angina was not influenced by the presence of complete or incomplete revascularisation after coronary angioplasty. This may be because the study group contained many patients with an occlusion elsewhere that had been present for a long time and was no longer causing symptoms.

After exclusion of patients who had had previous coronary artery bypass surgery, 76% of the patients who had a second coronary angioplasty because of a recurrence of the stenosis after a successful first procedure were angina free five years after the second procedure (mean follow up of only 17·4 months). This result is not statistically different from that (79 2%) in the patients who were symptoms free five years after a first coronary angioplasty.

ANGIOGRAPHIC FOLLOW UP

Angiographic follow up examination was performed in 728 (63%) of the 1163 patients in whom angioplasty had been initially successful a mean of 4·5 months before. In 98% of the symptom free patients who had angiographic follow up there was no restenosis. Twenty five per cent of the patients who had angiographic follow up had symptoms and 75% of these patients had angiographic evidence of recurrence. Of the patients who had no angiographic follow up, 96% were symptom free. Restenosis was seen 185 times in 174 (24%) patients. Even if a restenosis is defined as a stenosis of >50% of the luminal diameter, the restenosis rate remains approximately the same (177 times in 167 patients). Figure 2 shows the difference between the degree of stenosis immediately after and late after a successful dilatation. Of the 797 stenoses that were successfully dilated in these 728 patients, the main difference between the initial and follow up angiographic appearance was a mean (1SD) decrease in lumen diameter of 14·1 (29·0%). At repeat angiography 528 segments (66·2%) were unchanged (a change in diameter of ≥20% compared with the luminal diameter immediately after dilatation). These data suggest that the degree of stenosis at the end of the procedure does not predict the result at follow up angiography. Only two (8%) of the 25 patients who had two follow up angiograms had a late recurrence. Angiography at follow up showed progression of disease elsewhere in 10% of patients in whom angioplasty had been successful. There were no differences in the restenosis rate between patients with stable or unstable angina at the time of angioplasty. Repeat balloon dilatation was successful in 92% of 115 restenoses. Fifty one of these patients had angiographic follow up. A second restenosis occurred in 17 (33%) patients.

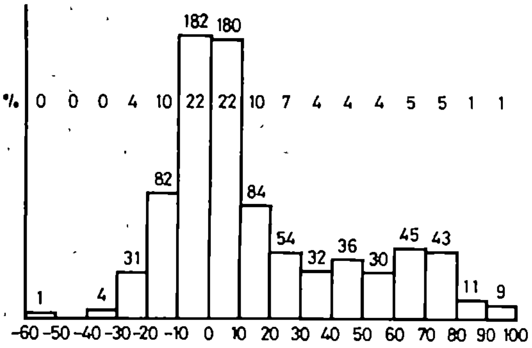

Fig 2 *The difference between the degree of stenosis immediately after and late after successful coronary angioplasty. When the stenosis decreased further with time the difference has a minus sign. Recurrences, therefore, are on the right hand side of this diagram.*

In 17 patients who had a successful coronary angioplasty immediately after thrombolytic treatment, 10 had a follow up angiogram and recurrences were seen in three. In 63 patients who had a successful coronary angioplasty some time after thrombolytic treatment, 46 had a follow up angiogram and recurrences were seen in seven (15·2%). Eight of the 11 patients with successful coronary angioplasty at the time of an acute myocardial infarction without thrombolytic treatment had a follow up angiogram and recurrences were seen in four (50%).

Discussion

Many reports indicate that balloon coronary angioplasty is effective in dilating coronary artery stenoses and relieving the associated symptoms of angina. This report suggests not only that short term but also that longer term relief of angina pectoris can be achieved. Patients who remain symptom free for the first six months after successful coronary angioplasty are likely to remain free of angina for the next five years. Only 2% of the symptom free patients who had repeat angiography showed evidence of restenosis without infarction or symptoms.

In the patients who have important restenosis at the site of the coronary angioplasty, anginal complaints usually recur within six months, whereas in the patients without angiographic evidence of recurrence but with considerable progression of the disease elsewhere symptoms usually occur later than one year after coronary angioplasty. This suggests that if symptoms recur after six months they are more likely due to progressive disease elsewhere rather than restenosis. This accords with the angina free curve after successful coronary angioplasty (without previous coronary artery bypass grafting) which demonstrates a rather steep drop to 87% in the first six months, after which the percentage of angina free patients drops to 81% over the next four and a half years. We do not know why 86% of our patients without previous coronary bypass surgery were symptom free after one year whereas in another report (from the Mayo Clinics) only 74% of similar patients remained free of angina after one year.[1] The medical treatment after coronary angioplasty is not specified in the Mayo Clinic report and it may be that differences in medical treatment have influenced the outcome in these two studies. Also the choice of the balloon size, pressure gradient determination at the end of the procedure, and other technical differences may influence the results. Reported percentages of angiographically proven recurrences of stenosis vary widely (range 12–47%)[2–4] and depend on the definition of restenosis. Systematic angiographic follow up data are generally lacking except in the studies of Kaltenbach *et al*[2,3] and Jutzy *et al*[5] and the percentage of patients with a follow up angiography in most other series varies widely. Patient selection must have influenced the percentage (24%) of angiographic recurrences in our series because patients with symptoms had repeat angiography more often than patients without (p < 0·001).

On the basis of intention to treat 1005 (14·3%) out of the original 1352 patients had a completely successful angioplasty. Neither the initial success rate nor the recurrence rates for angina pectoris, myocardial infarction, or angiographic restenoses were different in patients with stable or unstable angina at the time of coronary angioplasty. This accords with reports that coronary angioplasty is effective in patients with unstable angina that is refractory to medical treatment.[6,7] Our study was not designed to investigate the role of coronary angioplasty after thrombolytic treatment for acute myocardial infarction. In our series there was a high initial success rate for coronary angioplasty during acute myocardial infarction and immediately after thrombolytic treatment. It appears, however, that long term patency rates are higher if coronary angioplasty can be postponed for 12 hours or more after successful thrombolytic treatment.

If a restenosis occurs, a second coronary angioplasty can be performed effectively and safely in most cases. In the 115 restenoses for which a second coronary angioplasty was done, both the initial success rate (92%) and the late angiographic patency rate resemble those of the first coronary angioplasty. Forty eight months after the second dilatation 76% of these patients were angina free. This accords with the good results obtained with repeat coronary angioplasty in other series.[8]

Coronary artery bypass surgery was eventually performed in 158 (11·6%) patients—in 64 because of failure of the coronary angioplasty, in 36 (2·6%) because of an emergency during the angioplasty attempt, and in 58 because of recurrence of the stenosis and/or progression of the disease elsewhere after successful coronary angioplasty. These results indicate that angioplasty could prevent or postpone coronary bypass surgery in many patients with angina pectoris.

Conclusion

Angiographically successful coronary angioplasty offers a better chance of long lasting relief of symptoms than previously suggested. We do not know whether our figures were influenced more by the technical aspects than by medical treatment after angioplasty. If a restenosis occurs a second coronary angioplasty can be done with good initial and late results.

References

1 Mabin TA, Holmes DR, Smith HC, *et al*. Follow-up clinical results in patients undergoing percutaneous transluminal coronary angioplasty. *Circulation* 1985;71:754–60.

2 Kaltenbach M, Kober G, Schmidt-Moritz A, Scherer D. Rezidivhaufigkeit nach erfolgreicher transluminaler Koronarangioplastie. *Dtsch Med Wochenschr* 1983;**108**:1387–90.

3 Kaltenbach M, Kober G, Scherer D, Vallbracht C. Recurrence rate after successful coronary angioplasty. *Eur Heart J* 1985,**6**:276–81.

4 Dangoisse V, Val PG, David PR, *et al* Recurrence of stenosis after successful percutaneous transluminal coronary angioplasty (PTCA) [Abstract]. *Circulation* 1982;**66**(suppl II):331.

5 Jutzy KR, Berte LE, Alderman EL, Ratts J, Simpson JB. Coronary restenosis rates in a consecutive patient series one year post successful angioplasty [Abstract]. *Circulation* 1982;**66**(suppl II):331.

6 De Feyter PJ, Serruys PW, Van den Brand M, *et al.* Emergency coronary angioplasty in refractory unstable angina. *N Engl J Med* 1985,**313**.342–6

7 Meyer J, Schmitz HJ, Kiesslich T, *et al.* Percutaneous transluminal coronary angioplasty in patients with stable and unstable angina pectoris. analysis of early and late results. *Am Heart J* 1983;**106**:973–80.

8 Meier B, King SB III, Gruentzig AR, *et al* Repeat coronary angioplasty. *J Am Coll Cardiol* 1984;4: 463–6.

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Coronary haemodynamic effects of short term intravenous administration of gallopamil in patients with stable exertional angina

STEFANO DE SERVI, MAURIZIO FERRARIO, STEFANO GHIO, ANTONIO MUSSINI, LUIGI ANGOLI, EZIO BRAMUCCI, ANTONELLA BARTOLI,* ERCOLE POMA, RENATO RONDANELLI,* GIUSEPPE SPECCHIA

*From the Divisione di Cardiologia, *Dipartimento di Farmacologia, Policlinico S Matteo, Istituto di Ricovero e Cura a Carattere Scientifico, Pavia, Italy*

SUMMARY The effects of short term intravenous administration of gallopamil on coronary haemodynamic variables were studied in 10 patients with stable exertional angina and angiographically confirmed coronary artery disease that affected the proximal portion of the left anterior descending artery. Blood flow in the great cardiac vein was measured by a thermodilution technique, both at rest and during ischaemia induced by atrial pacing, before and after intravenous administration of gallopamil (0·02 mg/kg as a bolus dose given over three minutes, followed by an infusion of 0·0005 mg/kg/min). Gallopamil significantly prolonged the mean (SD) duration of pacing that was tolerated (11 (2·6) *vs* 14·8 (2·4)) min, significantly increased the mean (SD) peak heart rate attained during pacing (142 (15) *vs* 158 (11) beats/min), and reduced mean (SD) arterial pressure (133 (17) *vs* 116 (17) mm Hg). There were no changes in mean (SD) blood flow in the great cardiac vein (134·1 (57) *vs* 112·9 (38) ml/min, mean (SD) anterior regional coronary resistance (1·18 (0·6) *vs* 1·15 (0·5) mm Hg/ml/min), and mean (SD) anterior regional myocardial oxygen consumption (16·6 (6) *vs* 13·7 (4) ml/min).

These data confirm that gallopamil is an effective antianginal agent and suggest that a reduction of myocardial oxygen demand is the predominant mechanism by which the drug exerts its beneficial effects.

The antianginal efficacy of calcium channel blocking agents such as verapamil,[1-3] nifedipine,[4-6] and diltiazem[7-9] is well established. The mechanism of the effect depends on the affinity of the agent for its receptor sites and the cause of ischaemia, and is achieved by a reduction in myocardial oxygen consumption by an improvement in oxygen supply or both.

New calcium channel blocking agents are being developed to improve the efficacy and safety of antianginal action. One of these new calcium antagonists, gallopamil, a verapamil analogue, improved exercise tolerance in patients with stable exertional angina.[10-12] There is evidence that gallopamil exerts its antianginal effect by improving the ratio of myocardial oxygen supply to oxygen demand. But the mechanism of this action has not been elucidated.

We studied 10 patients with stable exertional angina and angiographically confirmed disease of the proximal portion of the left anterior descending coronary artery. Thermodilution measurements of blood flow in the great cardiac vein—that is the venous efflux from the territory supplied by the left anterior descending artery[13]—were taken at rest and during myocardial ischaemia induced by rapid atrial pacing both before and after the short term intravenous administration of gallopamil. The effects of the drug on pacing tolerance were then related to

Requests for reprints to Dr Stefano De Servi, Divisione di Cardiologia, Policlinico S Matteo, 27100 Pavia, Italy.

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coronary haemodynamic changes in the anterior region of the heart in which perfusion was jeopardised.

Patients and methods

PATIENTS

We studied 10 patients (nine men and one woman, mean age 54 years) with stable exertional angina. They all had a positive exercise test, defined as the development of typical chest pain associated with ST segment depression of >1 mm in the precordial leads. Patients with angina at rest or transient ST segment elevation during pain were excluded. No patient had a history of previous anterior myocardial infarction or showed abnormal Q waves in the precordial leads. The results of physical examination were normal. Left ventricular angiography and coronary arteriography showed significant coronary disease (stenoses of the luminal diameter >50%) of the proximal portion of the left anterior descending artery in all 10 patients.

We studied patients within two weeks of coronary arteriography, without premedication, and at least three days after *β* blockers had been progressively tapered and withdrawn. Withdrawal phenomena, such as accelerated angina or other acute coronary events, were not seen. Nifedipine and nitrates were discontinued for at least 12 hours. No patient was taking verapamil or diltiazem. We obtained the informed consent of all patients before the study.

METHODS

The study was performed late in the morning in supine fasting patients. A triple thermistor thermodilution catheter with pacing electrodes was introduced under local anaesthesia into an antecubital vein and advanced to the great cardiac vein. The position of the catheter was checked frequently by fluoroscopy during the procedure. Once the catheter was in position flow in the great cardiac vein while the patient was at rest was determined by a continuous infusion of a physiological saline solution (56 ml/min for 30 seconds). Arterial blood pressure was recorded continuously by means of a Teflon cannula in a brachial artery. Blood samples for the measurement of haemoglobin oxygen saturation were obtained from an artery and the great cardiac vein of nine patients. The heart rate was then increased by coronary sinus pacing, which increased by 10 beats per minute until the patient experienced chest pain or ST segment depression >2 mm developed in the anterior leads. Each pacing rate was maintained for two minutes. When the end point was reached, blood flow in the great cardiac vein was measured for 30 seconds in all patients and samples of arterial and great cardiac vein blood were again obtained in nine patients. A 12 lead electrocardiogram was recorded before and at the end of pacing, and leads V4, V5, and V6 were monitored throughout the test. After 40 minutes a bolus dose of gallopamil (0·02 mg/kg) was given intravenously over three minutes and this was followed by a continuous infusion of 0·0005 mg/kg/min. Ten minutes later baseline data were collected and atrial pacing was started again. When the patient experienced chest pain, when ST segment depression (>2 mm) developed, or when a heart rate of 170 beats per minute was reached, the coronary haemodynamic measurements were repeated. Venous blood samples for measuring gallopamil concentrations were also obtained at that time. An intravenous bolus dose (0·5 mg) of atropine was given to two patients in whom failure to capture occurred after gallopamil. No complications were observed during the pacing procedure.

Table 1 *Clinical, haemodynamic, and angiographic data in 10 patients with stable exertional angina*

Case No	*Sex*	*Age*	*LVEDP (mm Hg)*	*EF (%)*	*Stenosis of* *LAD*	*Cfx*	*RCA*
1	M	58	23	68	90%	—	—
2	M	60	13	59	75%	—	—
3	M	60	16	74	75%	90%	—
4	M	50	24	69	100%	—	99%
5	M	59	16	56	99%	90%	75%
6	M	49	7	84	99%	—	—
7	F	55	19	79	100%	75%	—
8	M	52	12	82	75%	—	—
9	M	51	14	70	75%	75%	100%
10	M	50	12	78	75%	99%	99%
Mean (SD)		54 (4)	16 (5)	72 (9)			

LVEDP, left ventricular end diastolic pressure, EF, ejection fraction; LAD, left anterior descending coronary artery; Cfx, circumflex; RCA, right coronary artery.

Table 2 *Resting values of haemodynamic variables in 10 patients with stable exertional angina*

	Heart rate (beats/min)		*MAP (mm Hg)*		*Double product (bpm × mm Hg × 10⁻²)*		*GCVF (ml/min)*		*ARCR (mm Hg/ml/min)*		*MVo₂ (ml/min)*	
Case No	*Control*	*GP*	*Control*	*GP*	*Control*	*GP*	*Control*	*GP*	*Control*	*GP*	*Control*	*GP*
1	71	75	129	121	139 2	137 2	58 8	63·4	2 19	1 9	5 3	5 3
2	108	102	141	131	209 5	191·8	104·3	104 3	1 35	1 25	13 1	12 9
3	73	85	120	102	124 8	120 7	93 5	89·8	1 28	1 13	9 7	9 7
4	58	65	110	102	93·4	92 9	43·2	36·9	2 54	2 76	6·9	5 8
5	82	76	134	117	150 9	130	91 3	62·3	1 47	1 88	12 6	8
6	60	63	104	104	100 2	92	52 8	58	1 97	1 79	6 9	6·7
7	113	103	129	96	206·8	141 1	52·8	30	2 44	3 2	6 8	3·4
8	72	72	108	125	113·8	116 6	82 4	128 7	1 31	0 97	10	15 5
9	70	66	100	96	114·1	101 6	45 6	50 3	2 19	1 91	—	—
10	67	71	100	92	91 8	94 4	56 9	43 9	1 76	2 1	6 8	4 9
Mean	77	78	117	109	134 4	121 8	68·2	66 8	1 85	1 89	8 7	8
(SD)	(19)	(14)	(15)	(14)	(43·2)	(30 7)	(22)	(31)	(0 5)	(0 7)	(3)	(4)

MAP, mean arterial pressure, GCVF, great cardiac vein flow, ARCR, anterior region coronary resistance; MVo^2, myocardial oxygen consumption; GP, gallopamil

There were no significant differences between control and gallopamil values.

CALCULATIONS AND STATISTICAL ANALYSIS

Great cardiac vein flow was calculated by thermodilution method by the formula:

$$\text{GCVF (ml/min)} = V_I \times \left(\frac{T_b - T_I}{T_b - T_m} - 1\right) \times 1{\cdot}08$$

where GCVF = great cardiac vein flow, V_I is the indicator rate of injection (56 ml/min), T_b is blood temperature, T_I is the temperature of injectate, and T_m is the temperature of the mixture of great cardiac vein blood and injectate; 1·08 is a constant related to the indicator.

Mean arterial pressure was measured by electronic filtration of the pressure curve and anterior regional coronary resistance was calculated as

$$\text{ARCR (mm Hg/ml/min)} = \frac{\text{MAP}}{\text{GCVF}}$$

where ARCR = anterior regional coronary resistance, MAP = mean arterial pressure, GCVF = great cardiac vein flow.

Anterior regional myocardial oxygen consumption was derived as (arterial oxygen content minus great cardiac vein oxygen content) × great cardiac vein flow. Heart rate was calculated from the electrocardiogram. Plasma gallopamil concentrations were measured by high performance liquid chromatography.

Statistical analysis was performed by Student's paired *t* test. All data are expressed as mean (SD).

Results

HAEMODYNAMIC AND ANGIOGRAPHIC FINDINGS

Four patients had disease of the proximal left ante-

Table 3 *Peak pacing values of haemodynamic variables in 10 patients with stable exertional angina*

	Heart rate (beats/min)		*MAP (mm Hg)*		*Double product (bpm × mm Hg × 10⁻²)*		*GCVF (ml/min)*		*ARCR (mm Hg/ml/min)*		*MVo² (ml/min)*	
Case No	*Control*	*GP*	*Control*	*GP*	*Control*	*GP*	*Control*	*GP*	*Control*	*GP*	*Control*	*GP*
1	130	140	165	137	297·7	268 8	125·8	125·8	1·31	1 08	10 7	10 7
2	150	160	143	133	291	288	146·3	141·1	0·97	0 94	17	16 7
3	150	160	118	110	238 5	235 2	149·1	135·8	0·79	0 81	16 6	16 3
4	120	150	137	110	216	220 5	59 8	45 2	2 29	2 43	9 3	6 7
5	150	160	137	125	274 5	267 2	186·6	102 6	0 73	1 22	22·8	13
6	140	170	133	96	256 2	227 8	171 9	138·4	0 77	0 69	20 1	17 7
7	160	170	125	92	273 6	227 8	63 8	80 7	1 96	1 14	7·4	10 8
8	160	160	146	142	307 2	280	236	176 3	0·62	0 81	26·9	20 7
9	120	140	108	108	200 4	221 2	73 5	84·6	1·47	1 28	—	—
10	140	160	117	108	221 2	233 6	128 6	98·6	0 91	1 1	14	10 5
Mean	142	158	133	116	257 6	247	134 1	112 9	1 18	1 15	16 1	13 7
(SD)	(15)*	(11)*	(17)†	(17)†	(37 1)	(26)	(57)	(38)	(0·6)	(0 5)	(6)	(4)

*$p < 0{\cdot}001$; †$p < 0{\cdot}005$

See footnote to table 2 for abbreviations.

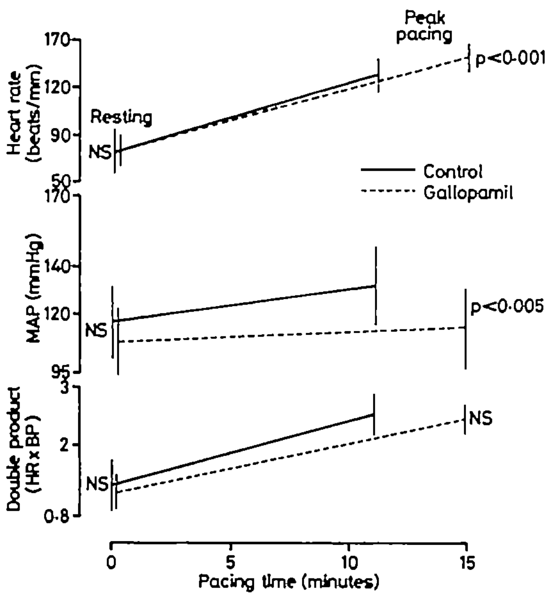

Fig 1 *Effects of gallopamil on heart rate, mean arterial pressure (MAP), and double product in 10 patients with stable exertional angina. Resting and peak pacing values are shown. No difference was observed at rest whereas heart rate increased and mean arterial pressure decreased at peak pacing after gallopamil had been given. As a result the double product remained unchanged; however, pacing was tolerated for longer after gallopamil.*

rior descending artery only, three had double vessel, and three had triple vessel disease (table 1). The mean ejection fraction was 0·72 (0·09) and the mean left ventricular end diastolic pressure was 16(5) mm Hg.

HAEMODYNAMIC AND METABOLIC EFFECTS OF GALLOPAMIL AT REST (TABLE 2)

The heart rate was unchanged after administration of the drug (77(19) *vs* 78(14) beats/min, p = NS). Mean arterial pressure fell in all but one patient (case no 8); however, the difference did not reach statistical significance (117(15) *vs* 109(14) mm Hg). As a consequence the double product decreased slightly and not significantly (134(42) *vs* 122(31) beats/min × mm Hg × 10^{-2}), as did anterior regional myocardial oxygen consumption (8·7(3) *vs* 8·0(4) ml/min, p = NS). No significant change was found in blood flow in the great cardiac vein (68·2(22) *vs* 66·8(31) ml/min) or anterior regional coronary resistance (1·85(0·5) *vs* 1·89(0·7) mm Hg/ml/min).

HAEMODYNAMIC AND METABOLIC EFFECTS OF GALLOPAMIL AT PEAK PACING (TABLE 3)

The end points of the coronary sinus pacing were angina in seven patients and ST segment depression of >2 mm without pain in the remaining three. After gallopamil only four patients complained of angina, five patients showed asymptomatic ST segment depression of >2 mm, and in one (case 6) pacing was stopped after the maximal pacing rate had been maintained for two minutes. In all but one patient (case 8) end points were reached at higher pacing rate after gallopamil (control 142(15), gallopamil 158(11) beats/min, p < 0·001). As a result gallopamil increased mean pacing time from 11·0(2·6) to 14·8(2·4) minutes (p < 0·001) while maximal ST segment depression decreased from 1·9 (0·5) to 1·6(0·7) mm (p = NS).

As mean arterial pressure decreased from 133(17) to 116(17) mm Hg (p < 0·005) the peak pacing double product was slightly but not significantly reduced (fig 1). There was no significant change in great cardiac vein flow or in anterior regional coronary resistance (fig 2). Anterior regional myocardial oxygen consumption was also unchanged after gallopamil (from 16·1(6) to 13·7(4) ml/min, p = NS).

The mean plasma concentration of gallopamil at peak pacing was 41·4 (13·8) ng/ml.

Discussion

Gallopamil is a new calcium antagonist with the structure of a phenylalkilamine derivative, like vera-

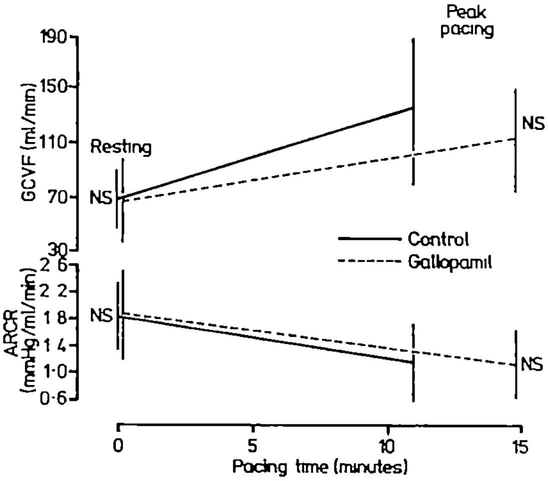

Fig 2 *Effects of gallopamil on great cardiac vein flow (GCVF) and anterior regional coronary resistance (ARCR) at rest and at peak pacing. No significant change was seen between resting values or peak pacing values.*

pamil. It has the same electrophysiological properties as verapamil, but is three to five times as potent on a weight for weight basis.[14] Oral gallopamil was as effective or more effective than propranolol in improving the exercise tolerance of patients with stable exertional angina after short term[11] and after long term administration.[10] Moreover, the drug is well tolerated; few adverse effects were reported after long term oral treatment.[10]

The mechanism by which this drug exerts its beneficial effects has yet to be established. After long term oral administration Khurmi *et al* found that the rate-pressure product at peak exercise was higher than after placebo.[10] Because the degree of ST segment depression was unchanged these workers suggested that the greater exercise capacity induced by gallopamil was the result of improved myocardial oxygen supply. By contrast, Rettig and Sen found that the double product did not increase at the end of exercise, either after short term or after long term oral administration.[12] Similarly, Scrutinio *et al* reported that the rate-pressure product was not modified at maximal workload[11]; this suggests that the drug may improve exercise capacity by reducing oxygen demand.

In our study short term intravenous administration of gallopamil improved pacing tolerance, confirming the antianginal activity of the drug. Because all patients had a proximal lesion of the left anterior descending artery we measured blood flow in the great cardiac vein, which is a reliable index of blood flow through that artery,[13 15 16] to assess haemodynamic changes in the area of the myocardium in which perfusion was jeopardised. Gallopamil did not increase blood flow in the great cardiac vein either at rest or at peak atrial pacing. Thus the beneficial effect of the drug does not seem to be related to increased perfusion of ischaemic regions. Moreover, myocardial oxygen consumption in the anterior region was similar at the peaks of the two pacing periods despite the higher heart rate that was achieved after gallopamil infusion. This suggests that the mechanism of action of the drug was a reduction in myocardial metabolic demand. Because most of our patients had multivessel disease, however, we cannot exclude the possibility that gallopamil increased blood flow to the non-anterior, yet potentially ischaemic myocardium and that such increase contributed to the improved performance induced by the drug. This possibility, however, seems remote, because the double product, a reflection of the maximal rate at which the obstructed coronary arteries deliver oxygen, was unchanged at peak pacing after gallopamil.

In conclusion, our data confirm that gallopamil is an effective antianginal drug that may well prove to be a useful addition to current treatment of angina pectoris. A reduction of myocardial oxygen consumption seems to be the predominant mechanism by which the drug exerts its beneficial effects.

References

1 Bala Subramanian V, Millar-Craig MW, Davies AB, Raftery EB. Verapamil therapy in variant angina: assessment by high-fidelity frequency modulated ambulatory ECG. *Am Heart J* 1981;**101**:849–50.

2 Bala Subramanian V, Paramasivan R, Lahiri A, Raftery EB. Verapamil in chronic stable angina: a controlled study with computerised treadmill exercise. *Lancet* 1980;**i**:841–4

3 Bala Subramanian V, Bowles M, Lahiri A, Davies AB, Raftery EB. Long-term antianginal action of verapamil assessed with quantitated serial treadmill stress testing *Am J Cardiol* 1981;**48**:529–35.

4 Antman E, Muller J, Goldberg S, *et al.* Nifedipine therapy for coronary-artery spasm. Experience in 127 patients. *N Engl J Med* 1980;**302**:1269–73.

5 Previtali M, Salerno JA, Tavazzi L, *et al.* Treatment of angina at rest with nifedipine: a short-term controlled study. *Am J Cardiol* 1980;**45**:825–30.

6 Specchia G, De Servi S, Falcone C, *et al.* Effects of nifedipine on coronary hemodynamic findings during exercise in patients with stable exertional angina. *Circulation* 1983,**68**:1035–43.

7 Pepine CJ, Feldman RL, Whittle J, Curry RC, Conti CR Effect of diltiazem in patients with variant angina: a randomized double-blind trial. *Am Heart J* 1981;**101**:719–25.

8 Bala Subramanian V, Khurmi NS, Bowles MJ, O'Hara M, Raftery EB. Objective evaluation of three dose levels of diltiazem in patients with chronic stable angina. *J Am Coll Cardiol* 1983;**1**:1144–53.

9 Hung J, Camb IH, Connolly SJ, Jutey KR, Goris ML, Schroeder JS. The effects of diltiazem and propranolol, alone and in combination, on exercise performance and left ventricular function in patients with stable effort angina: a double-blind, randomized and placebo-controlled study. *Circulation* 1983; **68**:560–7.

10 Khurmi NS, O'Hara MJ, Bowles MJ, Bala Subramanian V, Raftery EB. Randomized double-blind comparison of gallopamil and propranolol in stable angina pectoris. *Am J Cardiol* 1984;**53**:684–8.

11 Scrutinio D, Lagioia R, Accettura D, Preziusi N, Mastropasqua E, Rizzon P. Dose-response effectiveness of gallopamil for the treatment of chronic stable effort angina pectoris: comparison with propranolol. *Curr Ther Res* 1985;**37**:830–8.

12 Rettig G, Sen S. Acute and long-term effects of gallopamil in patients with stable angina pectoris. In: Kaltenbach M, Hopf R, eds. *Gallopamil. Pharmacological and clinical profile of a calcium antagonist.* Berlin, Heidelberg, New York, Tokyo: Springer-Verlag, 1984:136–42.

13 Roberts DL, Nakazawa HK, Klocke FJ. Origin of great cardiac vein and coronary sinus drainage within the left ventricle. *Am J Physiol* 1976;230:486–92.

14 Fleckenstein A, Fleckenstein B, Spah F, Byon YK. Gallopamil (D-600)—a calcium antagonist of high potency and specificity. Effects on the myocardium and pacemakers. In: Kaltenbach M, Hopf R, eds. *Gallopamil. Pharmacological and clinical profile of a calcium antagonist.* Berlin, Heidelberg, New York, Tokyo: Springer-Verlag, 1984:1–32.

15 Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation* 1971;44.181–95.

16 Pepine CJ, Metha J, Webster WW Jr, Nichols WW. In vivo validation of a thermodilution method to determine regional left ventricular blood flow in patients with coronary disease. *Circulation* 1978;58:795–802.

Br Heart J 1987;57:232–6

Sex differences in exercise induced left ventricular dysfunction in patients with syndrome X

LUIGI FAVARO,† JOHN L CAPLIN, JURE J FETTICHE,* DUNCAN S DYMOND

*From the Departments of Cardiology and *Nuclear Medicine, St Bartholomew's Hospital, London*

SUMMARY Clinical, electrocardiographic, and scintigraphic data were reviewed from 32 patients (18 men and 14 women) who had syndrome X (chest pain, evidence of ischaemia, and normal coronary arteries without coronary vasospasm). The mean (SD) resting left ventricular ejection fraction, determined by first pass radionuclide angiography was 62·6 (9·2)% and was $>50\%$ in all subjects. There was no significant difference between men and women. On exercise, left ventricular ejection fraction decreased significantly to 57·4 (13·0)%. In 17 of 32 subjects there was a fall in left ventricular ejection fraction of $>5\%$, and regional wall motion abnormalities developed in 12 subjects. The fall in left ventricular ejection fraction on exercise was significant in women (from 61·9 (8·5)% at rest to 54·0 (9·8)% on exercise) but not in men (from 63·2 (9·8)% at rest to 60·0 (14·8)% on exercise). Exercise left ventricular ejection fraction fell by $>5\%$ in 10 (71%) of 14 women and in seven (39%) of 18 men. Dyskinetic segments developed in eight (57%) of 14 women and only four (22%) of men. Exercise duration in women was significantly shorter than in men (4·1 (1·5) *vs* 6·6 (2·1) minutes) and was the only one of several clinical and scintigraphic variables that correlated with the change in left ventricular ejection fraction on exercise.

In this selected group of subjects with chest pain and angiographically normal coronary arteries, exercise induced left ventricular dysfunction, as shown by a fall in ejection fraction or the development of regional abnormalities, is a common finding. These are more likely to occur in women than men and are associated with a lower exercise capacity. The data suggest that the sex of the patient is important in the interpretation of the non-invasive evaluation of subjects suspected of having syndrome X.

Most of the clinical manifestations of ischaemic heart disease are due to fixed or dynamic obstruction of epicardial coronary arteries. Coronary angiography remains the gold standard by which normality or abnormality of the coronary circulation is judged and its importance in clinical decision making and prognosis cannot be denied.[1]

None the less, there is a subset of patients in whom there is evidence of ischaemia in the absence of abnormal coronary arteriograms or evidence of coronary vasospasm. This clinical group has been labelled as syndrome X.[2] These patients have functional rather than anatomical ischaemia and are particularly difficult to manage. They have been investigated by various invasive and non-invasive methods.

This study assessed the frequency of exercise induced left ventricular dysfunction in a group of these patients and examined the differences in response between male and female patients.

Patients and methods

STUDY POPULATION

The records of 174 patients were reviewed. They had been referred to the Nuclear Cardiology Laboratory in the years 1982–86 and had undergone (within one year) both coronary arteriography for a primary diagnosis of possible ischaemic heart disease and exercise radionuclide angiography. One hundred and thirty five patients with obstructive co-

Requests for reprints to Dr John L Caplin, Department of Cardiology, Southampton General Hospital, Tremona Road, Southampton SO9 4XY

†Present address Division of Cardiology, Ospitale di Parma, Via Gramsci, Parma, Italy.

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ronary artery disease (lesions of $>25\%$ luminal diameter) were excluded, which left 39 patients with normal coronary and left ventricular angiograms. Seven further patients were subsequently excluded: two had documented myocardial infarction; two had coronary ectasia; one each had aortic stenosis, hypertrophic cardiomyopathy, and mitral valve prolapse. We studied the remaining 32 patients (18 men and 14 women). All had either typical anginal pain (defined as exercise or emotion induced central crushing chest pain with or without radiation to the arms or jaw), or had atypical chest pain (defined as chest pain without classic anginal features but warranting invasive cardiac investigation). No patient had a history suggestive of variant angina and none had spontaneous coronary vasospasm documented during coronary angiography. Provocation testing for coronary vasospasm was not performed in our laboratory.

CORONARY ANGIOGRAPHY

Cardiac catheterisation was performed by either the brachial or femoral artery techniques. Multiple views of each coronary artery were assessed by an experienced observer, and subjects were selected on the basis of having normal or minor irregularities (luminal narrowing $<25\%$) of the coronary arteries only. All coronary arteriograms and left ventricular angiograms were reviewed and subjects with coronary ectasia, muscle bridges, coronary vasospasm, or mitral valve prolapse at the time of catheterisation were excluded.

RADIONUCLIDE ANGIOGRAPHY AND EXERCISE PROTOCOL

All antianginal medications were discontinued at least 72 hours before the study. First pass radionuclide angiography was performed with a multicrystal gamma camera (Baird Atomic System–77) as previously described.[3] The patients were imaged in the upright anterior-posterior projection at rest and at then at peak exercise on an hydraulically braked bicycle ergometer (Fitron). Exercise started at a workload of 400 kpm/minute (66 8 W) and increased by 200 kpm/minute (33·4 W) every two minutes until a symptom limited peak was reached. A total of 950 MBq (26 mCi) of technetium-99m as pertechnetate was injected for the entire study. The electrocardiogram (lead II) was monitored throughout the test, and rest and peak exercise heart rate and total exercise duration were noted.

Left ventricular ejection fraction was calculated from high frequency time-activity curves by a semi-automated method, and regional wall motion was assessed from count-based regional ejection fraction images. The left ventricular border was visually divided into three equal segments—inferior, apical, and anterior—and a segment was deemed to be abnormal if at least half of it had a regional ejection fraction of $<50\%$.[4]

STATISTICAL ANALYSIS

Results are expressed as mean (SD). Changes within groups were analysed by a paired t test and between groups by an unpaired t test, or χ^2 tests as appropriate. Correlation coefficients (r) were derived on a microcomputer with a standard software program. A p value of $<0{\cdot}05$ was regarded as significant.

Results

CLINICAL AND ANATOMICAL DATA

Table 1 shows the data for the entire group and for men and women separately. There were no significant differences between men and women in age, the distribution of typical angina or atypical chest pain, abnormalities on resting or exercise electrocardiography, or the numbers of subjects with minor coronary irregularities.

The main indication for coronary angiography was typical angina in 14 patients (eight men and six women) and atypical chest pain in 18 patients (10 men and eight women). Resting electrocardiography

Table 1 *Clinical and investigation data in patients with syndrome X*

Data	*Total*	*Men*	*Women*
Number	32	18	14
Mean (SD) age (years)	48 2 (8 8)	46 5 (9 4)	50 5 (7 9)
Typical angina (%)	44	44	43
Atypical chest pain (%)	56	56	57
Abnormal rest ECG (%)	19	11	29
Abnormal exercise ECG (%)	41	39	43
Minor coronary lesions (%)	13	17	7

ECG, electrocardiogram

Table 2 *Results (mean (SD)) of the radionuclide rest and exercise studies in patients with syndrome X*

Variable	*Total*	*Men*	*Women*
Rest HR (beats/min)	78 5 (17 1)	72 8 (12 7)	85·7 (19 6)*
Exercise HR (beats/min)	159 0 (20 0)	155 1 (18 8)	163 9 (21 2)
Exercise time (min)	5 5 (2 2)	6 6 (2 1)	4 1 (1 5)†
Rest EF (%)	62 6 (9 2)	63 2 (9 8)	61 9 (8 5)
Exercise EF (%)	57 4 (13 0)‡	60 0 (14 8)	54 0 (9 8)‡
ΔEF (%)	− 5 2 (10 6)	− 3 2 (11 7)	− 7 8 (8 7)

HR, heart rate, EF, left ventricular ejection fraction, Δ, difference between rest to exercise.
*p <0 05 *vs* males; †p <0 01 *vs* males; ‡p <0 01 *vs* rest

Table 3 *Number (%) of subjects in each group with an abnormal left ventricular ejection fraction response to exercise (fall of ≥5%), an abnormal exercise left ventricular ejection fraction (<50%), and the development of wall motion abnormalities (see text for definitions)*

Variable	*Total*	*Men*	*Women*
No	32	18	14
Abnormal EF response	17 (53%)	7 (39%)	10 (71%)
Abnormal exercise EF	12 (37%)	5 (27%)	7 (50%)
Wall motion abnormality	12 (37%)	4 (22%)	8 (57%)

See tables 1 and 2 for abbreviations

was abnormal in six patients: two had inferolateral ST-T segment changes, one had intermittent left bundle branch block, and three had incomplete right bundle branch block. Twenty patients (11 men and nine women) had treadmill exercise electrocardiographic tests; 13 (seven men and six women) were abnormal, with the development of > 1 mm of horizontal or downsloping ST segment depression 0·08s after the J point. Four patients (three men) had minor coronary irregularities.

REST AND EXERCISE RADIONUCLIDE DATA

Table 2 shows the results derived from the radionuclide studies at rest and during exercise for all the patients, and for the groups of men and women. All patients had normal resting left ventricular ejection fraction (> 50%) and all had normal resting regional left ventricular function. On exercise, left ventricular ejection fraction fell significantly (p < 0·01) for the whole group; and this was almost entirely due to the fall in women (p < 0·01). Women also had a higher resting heart rate than men (p < 0·05) and a lower total exercise duration (p < 0·01).

Table 3 shows the frequency of abnormal left ventricular ejection fraction responses (falls of >5% below the resting value), the number of patients with an exercise left ventricular ejection fraction below the normal range for our laboratory (<50%), and the frequency of regional dysfunction on exercise. Seventeen (53%) of the group had an abnormal global response (71% of women and 39% of men). Half the women but only 27% of the men had an abnormal exercise left ventricular ejection fraction. Regional wall motion abnormalities developed in 12 of the 17 patients with an abnormal global response. A total of 27 segments became abnormal in eight (57%) women and four (22%) men.

Table 4 *Clinical and radionuclide data arranged according to the response of left ventricular ejection fraction to exercise*

	Response of left ventricular ejection fraction to exercise	
	Normal	*Abnormal (fall ≥5%)*
No	15	17
Mean (SD) age (years)	43 8 (8 9)	52 4 (6 6)†
Typical angina [%]*	7 [47]	7 [41]
Atypical chest pain [%]*	8 [53]	10 [59]
Minor coronary lesion [%]*	3 [20]	1 [6]
Mean (SD) exercise time (min)	6 3 (2 4)	4 9 (1 9)
Mean (SD) rest EF (%)	63 9 (10 4)	61 5 (8 1)

*Percentage of each group.
†p < 0 01 *vs* normal response
See table 2 for other abbreviations

Table 5 *Clinical and radionuclide data in patients with symptoms of typical angina or with atypical chest pain*

	Chest pain	
Variable	*Typical*	*Atypical*
No	14	18
Men [%]	8 [57]	10 [56]
Age (years)	47 0 (8 3)	49 2 (9 4)
Exercise time (min)	5 7 (2 0)	5 4 (5 4)
Rest EF (%)	64 4 (10 2)	61 3 (8 3)
Exercise EF (%)	60 2 (14 4)	55 2 (11 8)
ΔEF (%)	−4 1 (8 1)	−6 1 (12 4)

See tables 2 and 4 for abbreviations.

Of five clinical and radionuclide variables (age, resting and exercise heart rate, exercise duration, and resting ejection fraction) examined for evidence of univariate correlation with the response of the ejection fraction to exercise, only the exercise duration had any significant linear correlation (r = 0 4052, p < 0·05); but as indicated by the low coefficient this was relatively weak.

When the data were reanalysed independently of sex and according to the normality or abnormality of the response of the global ejection fraction to exercise (table 4) the only significant difference between the groups was that an abnormal response was commoner in older subjects (p < 0·01). There were, however, no significant differences between the

Table 6 *Clinical and radionuclide data in the 20 patients with either a positive or a negative exercise electrocardiogram. An abnormal EF response was a fall of ≥5% in ejection fraction from rest to exercise and an abnormal exercise EF was an absolute EF<50%*

	Exercise electrocardiogram	
Variable	*Positive*	*Negative*
No	13	7
Men [%]	7 [54]	4 [57]
Typical angina [%]	6 [46]	2 [29]
Mean (SD) age (years)	49 9 (7 1)	51 9 (5 6)
Mean (SD) rest EF (%)	63 5 (11 0)	57 8 (9 5)
Mean (SD) exercise EF (%)	57 3 (15 0)	56 0 (13 9)
ΔEF (%)	− 6 2 (9 6)	− 1 7 (6 0)
Abnormal EF response [%]	8 [61]	4 [57]
Abnormal exercise EF [%]	4 [31]	3 [43]

See tables 2 and 4 for abbreviations.

groups with typical or atypical chest pain (table 5). Of the four patients with minimal anatomical irregularities, only one had an abnormal ejection fraction response to exercise.

Of the twenty subjects who had an exercise electrocardiogram, 13 were abnormal and seven were normal. Table 6 shows the distribution of clinical and radionuclide variables in these groups. There were no significant differences in either clinical or functional variables between subjects with a normal or abnormal exercise electrocardiogram.

Discussion

Syndrome X, as its name implies, remains an enigma. The combination of angina and evidence of "ischaemia" on non-invasive or invasive testing, in the presence of normal or near normal coronary arteries, is one of the most difficult management problems in adult cardiology. Many methods have been used to investigate its pathophysiology, often with conflicting results.

Left ventricular end diastolic pressure has been found to decrease[5] and angiographic left ventricular ejection fraction to increase[6] after atrial pacing in the patients with syndrome X but not in patients with fixed coronary stenoses. Some investigators have been unable to induce any abnormalities of left ventricular contractility, but abnormalities in myocardial lactate production have been demonstrated in some patients,[7] while others have reported significant left ventricular dysfunction after isometric exercise.[8] Although "small vessel" coronary artery disease has been suggested as the condition underlying syndrome X, Opherk *et al* have been unable to demonstrate any ultrastructural changes, even in subjects who showed a considerable impairment of coronary vasodilator reserve in response to dipyridamole.[8] Dynamic abnormalities of the coronary microcirculation have been invoked as an explanation.[9]

This study has assessed the extent of exercise induced left ventricular dysfunction in a selected subset of patients with the clinical and investigational features of syndrome X. Left ventricular dysfunction occurred on exercise in 53% of the subjects and there was a significant fall in mean ejection fraction. Reanalysis according to sex showed that the main abnormalities in the group occurred in women—71% had an abnormal left ventricular response to exercise. Patients with abnormal responses to exercise were significantly older than those with normal responses. These data are supported by the study of Port *et al* who found impairment of the "normal" left ventricular response to exercise in older subjects.[10] Although the women were on average older than the men in our study this difference was not statistically significant and is unlikely to be the explanation for the observed differences in left ventricular function between the sexes.

We were unable to demonstrate any differences between subjects with or without typical angina, and this contrasts with a study by Cannon *et al*, who demonstrated significantly lower increases in coronary flow and significantly greater increases in left ventricular end diastolic pressure after atrial pacing in syndrome X patients with typical angina than in those with atypical pain.[9]

It has been reported that up to 40% of patients with syndrome X have some degree of left ventricular dysfunction at rest,[11] and a similar proportion have been shown to have abnormalities on exercise[12]; however, this conflicts with some earlier reports where all subjects with normal coronary arteries behaved "normally".[13] The variation in these results may be explained by differences in study population such as age, sex, and entry criteria. In a recent study that assessed the time course of changes in left ventricular function on exercise by rapid sequential first pass radionuclide angiography with gold-195m we found an overall increase in ejection fraction on exercise in patients with normal coronary arteries; however, all the subjects were male.[3]

This study has shown that patients with syndrome X are a non-homogeneous group and that in this group women are more likely than men to develop left ventricular dysfunction on exercise. Previous studies have also shown that falls in left ventricular ejection fraction and the development of wall motion abnormalities are associated with a reduced exercise capacity in women,[14] and this is confirmed by the current data. No other previous studies have specifically examined the differences in left ventricular responses between men and women with normal coronary arteries or with syndrome X.

The possibility remains that the observed changes in left ventricular function are a result of exercise induced coronary artery spasm.[15] None of the subjects had variant angina and none had spasm during coronary arteriography. Provocation tests are not routinely performed in our laboratory, but in a study of patients with syndrome X challenged with ergometrine maleate there were no significant changes in luminal diameter of major coronary arteries. This was found in subjects with both typical and atypical chest pain.[9] These data suggest that reactivity in large epicardial vessels is not altered in patients with syndrome X.

A higher frequency of syndrome X in women was originally reported,[5] although subsequently the imbalance was less in larger studies.[9] The specificity of thallium-201 myocardial scintigraphy is less in women than in men.[16] This is mainly attributed to attenuation in the breast tissue causing false positive scans, but the current findings suggest that the higher frequency may be associated with true abnormalities of global and regional left ventricular function in women with normal coronary arteriograms. Data to support this hypothesis have recently been presented by Legrand *et al*, who found that abnormalities in regional ventricular function on exercise in patients with syndrome X correlated with abnormalities of flow in the same segment.[17] Thus our findings may indicate a higher frequency of true perfusion abnormalities in women.

In conclusion, we found that left ventricular dysfunction on exercise was common in patients with syndrome X. It is more likely to occur in women and in older subjects. Because there are differences in the left ventricular response to exercise in syndrome X the sex of the patient should be considered when non-invasive investigations for suspected coronary artery disease are evaluated.

References

1 The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group. Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina. *N Engl J Med* 1984;**311**:1333–9.

2 Opherk D, Zebe H, Weihe E, *et al*. Das Syndrome pektanginoser beschwerden bei Patienten mit normalen Koronarogramm (Syndrom X). *Dtsch Med Wochenschr* 1981;**106**:1686–91.

3 Caplin JL, Dymond DS, O'Keefe JC, *et al*. Relation between coronary anatomy and serial changes in left ventricular function on exercise: a study using first pass radionuclide angiography with gold-195m. *Br Heart J* 1986;**55**:120–8.

4 Dymond DS, Foster C, Grenier RJ, Carpenter J, Schmidt DH. Peak exercise and immediate postexercise imaging for the detection of left ventricular function abnormalities in coronary artery disease. *Am J Cardiol* 1984;**53**:1532–7.

5 Arbogast R, Bourassa MG. Myocardial function during atrial pacing in patients with angina pectoris and normal coronary arteriograms. *Am J Cardiol* 1973; **32**:257–63.

6 Mammohansingh P, Parker JO. Angina pectoris with normal coronary arteriograms: hemodynamic and metabolic response to atrial pacing. *Am Heart J* 1975;**90**:555–61.

7 Boudoulas H, Cobb TC, Leighton RF, Wilt CM. Myocardial lactate production in patients with angina-like chest pain and angiographically normal coronary arteries and left ventricle. *Am J Cardiol* 1974;**34**: 501–5.

8 Opherk D, Zebe H, Weihe E, *et al*. Reduced coronary dilatory capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. *Circulation* 1981; **63**:817–25.

9 Cannon RO, Leon MB, Watson RM, Rosing DR, Epstein SE. Chest pain and "normal" coronary arteries—role of small coronary arteries. *Am J Cardiol* 1985;**55**:50–60B.

10 Port S, Cobb FR, Coleman E, Jones RH. Effect of age on the response of the left ventricular ejection fraction to exercise. *N Engl J Med* 1980;**303**:1133–7.

11 Altieri PI, Pollack MEM, Leighton RF. Left ventricular dysfunction in patients with angina-like chest pain and angiographically normal coronary arteries [Abstract]. *Am J Cardiol* 1975;**35**:118.

12 Gibbons RJ, Lee KL, Cobb F, Jones RH. Ejection fraction response to exercise in patients with chest pain and normal coronary arteriograms. *Circulation* 1981;**64**:952–7.

13 Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS. Real-time radionuclide cineangiography in the non-invasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. *N Engl J Med* 1977;**296**:839–44.

14 Jones RH, McEwan P, Newman GE, *et al*. Accuracy of diagnosis of coronary artery disease by radionuclide measurement of left ventricular function during rest and exercise. *Circulation* 1981;**64**:586–601.

15 Caplin JL, Banim SO. Chest pain and electrocardiographic ST-segment elevation occurring in the recovery phase after exercise in a patient with normal coronary arteries. *Clin Cardiol* 1985;**8**:228–9.

16 Okada RD. Value and limitations of myocardial scintigraphy with thallium-201 and long chain fatty acids for the detection of coronary artery disease. In: Simoons ML, Reiber JHC, eds. *Nuclear imaging in clinical cardiology*. Boston: Martinus Nijhoff, 1984: 55–82.

17 Legrand V, Hodgson JMcB, Bates ER, *et al*. Abnormal coronary flow reserve and abnormal radionuclide exercise test results in patients with normal coronary angiograms. *J Am Coll Cardiol* 1985;**6**:1245–53.

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Prediction of coronary artery disease by left ventricular regional wall motion abnormalities in patients with stenosis of the aortic valve

ROBERT E SAFFORD, ALFRED A BOVE

From the Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA

SUMMARY To identify predictive factors for coronary artery disease in patients with stenosis of the aortic valve the clinical histories, haemodynamic measurements, biplane contrast left ventriculograms, and coronary angiograms of 83 consecutively catheterised patients with valvar aortic stenosis were examined retrospectively. The mean (SD) age was 66 4 (9·1) years and 78% were men. Fifty five patients had significant coronary artery disease (⩾50% diameter narrowing). Forty five (82%) of 55 patients with and 23 (82%) of 28 patients without coronary disease had angina. Heart failure occurred in a third of the patients; these patients were on average older, were more likely to be female, and had lower ejection fractions and cardiac outputs than patients in whom failure did not occur. Calculated valve area, transvalvar gradient, and left ventricular end diastolic pressure did not discriminate between patients with and without coronary disease. Syncope was less common than angina and heart failure and was associated with significantly lower valve areas and higher gradients than those found in patients without syncope. Left ventricular regional wall motion abnormalities were equally common in the groups with and without angina and predicted coronary artery disease with 94% accuracy. The absence of regional wall motion abnormality was an insensitive marker of normal coronary arteries as 45% of such patients had coronary disease. Five of the 83 patients had significant coronary disease without angina or regional wall motion abnormality.

In patients with aortic stenosis angina did not predict the presence of coronary artery disease; therefore, it is advisable to have the results of coronary angiography before aortic valve replacement in a population such as this. Two of the patients with heart failure and severe aortic stenosis had regional wall motion abnormality with normal coronary arteries. Thus in some patients left ventricular failure produced by increased afterload may itself be a cause of left ventricular regional wall motion abnormality.

Left ventricular function in patients with stenosis of the aortic valve has been a subject of considerable interest. Previous studies have focused on correlating the severity of aortic valve obstruction with the presence of symptoms, the influence of concomitant coronary artery disease on symptoms,[1–3] mechanisms that compensate for increased afterload,[4–6] and the relation of preoperative global left ventricular function to perioperative survival and long term results after aortic valve replacement.[7]

Since most patients with aortic stenosis are elderly they are at risk for coronary artery disease. Angina is a common symptom in patients with aortic stenosis. Several studies have shown that the percentage of patients with angina at the time of aortic valve replacement for aortic stenosis ranges from 40% to 90%.[1 2 8] Graboys and Cohn evaluated 19 patients with aortic stenosis and found that 12 of them had angina but only four of the 12 had coronary artery disease.[1] They felt that the absence of angina virtually excluded coronary artery disease. Similar con-

Requests for reprints to Dr Robert E Safford, Division of Cardiovascular Diseases, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida 32224, USA.

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clusions were reached by Storstein and Enge who found that 40 of 44 patients with aortic stenosis had angina but only 12 had coronary artery disease.[8] Liedtke *et al* found that in patients with aortic stenosis the frequency of angina was unchanged by the presence of coronary artery disease.[9] Thus aortic stenosis alone was a common cause of myocardial ischaemia, and the presence of angina in a patient with aortic stenosis was not helpful in deciding whether the patient had concomitant coronary artery disease. On the other hand, Paquay *et al* found that 18 of their 19 patients with aortic stenosis who did not have chest pain were free of important coronary artery disease and they concluded that the absence of angina and electrocardiographic abnormalities suggesting myocardial infarction virtually excluded important coronary artery disease.[2]

The question whether regional wall motion abnormalities of the left ventricle are always due to concomitant coronary artery disease or whether they can develop as part of left ventricular failure independently of coronary artery disease is unresolved. St John Sutton *et al,* who studied patients with hypertrophic obstructive cardiomyopathy,[10] and Osbakken *et al,* who studied patients with aortic or mitral regurgitation,[11] both found that regional wall motion abnormalities appeared in association with left ventricular failure in patients without coronary artery disease. In the current study we have examined the relation between regional wall motion abnormalities of the left ventricle and coronary artery disease in patients with aortic stenosis.

Patients and methods

To assess the influence of coronary artery disease on regional wall motion of the left ventricle in patients with stenosis of the aortic valve we retrospectively reviewed the symptoms, haemodynamic data, biplane contrast left ventriculograms, and coronary cineangiograms of 83 consecutively catheterised patients with aortic stenosis. Fifty five had coronary artery disease; none had other clinically significant valve lesions or an intracardiac shunt. All of the patients were catheterised between May 1981 and November 1982 in the same laboratory.

Eleven other patients were excluded because of incomplete angiographic studies. All 11 had coronary angiography and measurement of the aortic transvalvar pressure gradient, but left ventriculograms were not obtained. This group had clinically obvious severe aortic stenosis, and catheterisation was performed to search for coronary artery disease. Left ventriculograms were not performed in these cases because echocardiography or radionuclide ventriculography had been used to assess systolic function before catheterisation or because the angiographer considered that haemodynamic decompensation was likely to occur with the contrast load.

Catheterisation was performed via a right antecubital cut down and brachial arteriotomy using the Sones' technique. Aortic root and left ventricular pressures were measured with a Lehman catheter. Other than measurement of pressure left ventricular diastolic function was not examined. In 75 of the 83 cases the cardiac output was measured via the indicator dilution technique with injections of indocyanine green into the left ventricle and sampling from the left brachial artery. In the remaining eight cases the cardiac output was not measured, and hence the aortic valve area could not be calculated. Systemic arterial pressure was also measured continuously via the left brachial catheter. The area of the aortic valve orifice was estimated in square centimetres from the ratio of the calculated cardiac output in litres per minute to the square root of the peak to peak pressure gradient (mm Hg) between the left ventricle and aortic root.[12] Biplane contrast left ventriculograms were obtained in the 30° right anterior oblique and 60° left anterior oblique projections usually with the injection of 35–45 ml of Renografin-76 over three seconds via a power injector. Ventriculography was performed before coronary angiography and the ventriculograms were interpreted qualitatively by concensus by two experienced angiographers before the coronary angiograms were interpreted. Regional wall motion abnormalities were detected visually and were localised and graded by the schema for the national Coronary Artery Surgery Study.[13]

Coronary angiography was performed using multiple views of the left coronary artery, including both cranial and caudal angulation, and at least one view of the right coronary artery. Significant coronary artery disease was defined as at least one stenosis causing narrowing of at least 50% of the diameter of the left main, left anterior descending, circumflex, or right coronary arteries or one of their diagonal, marginal, posterior descending, posterolateral, or intermediate branches. The degree of stenosis was estimated visually in the projection showing the greatest stenosis and the nearest segment of coronary artery of normal appearance was taken as the point of reference. To minimise bias in the assessment of regional wall motion abnormalities of the left ventricle by previous knowledge of the coronary anatomy coronary angiograms were interpreted after interpretation of the left ventriculogram.

Symptoms were assessed from the history obtained by the consulting cardiologist and included angina pectoris, heart failure, and syncope, or pre-syncope. The diagnosis of heart failure required one or more of the following signs or symptoms: elevated jugular venous pressure, pulmonary oedema on chest *x* ray, rales that did not clear with cough, orthopnoea, or paroxysmal nocturnal dyspnoea. Because of the difficulty in differentiating dyspnoea on exertion caused by heart failure from that associated with angina pectoris during exertion or that caused by lung disease or obesity, exertional dyspnoea by itself was not accepted as evidence of heart failure. Of the 26 patients judged to have heart failure on clinical grounds, 11 had documented pulmonary oedema, five had paroxysmal nocturnal dyspnoea without pulmonary oedema, and 17 were taking digitalis (three patients), a diuretic (five patients), or both (nine patients). Two of the 11 patients with pulmonary oedema received no pharmacological treatment before catheterisation. χ^2 tables and *t* tests were used to compare various subsets of the data.[14]

Results

SYMPTOMS

Table 1 summaries the characteristics of the study population. Among adults valvar aortic stenosis severe enough to require valve replacement is predominantly a disease of elderly men. The mean age of the patients was 66·4 years at the date of catheterisation and 78% were men. Nearly two thirds (66·2%) of the patients had coronary heart disease and they were, on the average, four years older than those who did not. Angina was the most common symptom and occurred in 45 (82%) of the 55 patients with important coronary artery disease and 23 (82%) of 28 without important coronary artery disease. Table 2 shows that in patients with angina and those without angina mean values for left ventricular systolic function (ejection fraction), cardiac output, left ventricular end diastolic pressure, and severity of aortic stenosis (as judged by gradients and calculated valve areas) were similar. Regional wall motion abnormalities were equally common in the groups with angina and without angina.

Heart failure was present in nearly a third of the patients (26 of 83, 31·3%). Table 3 shows that these patients were significantly older and more likely to be female than patients without failure, though men still predominated (18 M, 8 F). As would be expected, those with heart failure tended to have higher left ventricular filling pressures (despite treatment with digitalis, diuretics, or both in most cases) and lower ejection fractions than patients without failure. The difference in ejection fraction was statistically significant ($p < 0·05$) but the difference in left ventricular filling pressure was not. The calculated valve areas and transvalvar gradients were comparable though the cardiac outputs of patients with heart failure were on average lower than those of patients without heart failure ($p = 0·04$ for single tailed *t* test and 0·08 for two tailed *t* test). Similar percentages of the groups with and without

Table 1 *Haemodynamic variables (mean (SD)) in all study patients with aortic valve stenosis*

Variable	
No of patients (sex)	83 (65 M, 18 F)
Age (yr)	66·4 (9·1) (range 33–85)
No with significant CAD	55
LV ejection fraction (%)	58 (15)
LVEDP (mm Hg)	23 (10)
Gradient (mm Hg)	69 (30)
Cardiac output (l/min)	5·2 (1·4) (n = 75)
Calculated valve area (cm²)	0·67 (0·25) (n = 75)
No with RWMA	32

RWMA, regional wall motion abnormality of the left ventricle; CAD, coronary artery disease, LV, left ventricular; LVEDP, left ventricular end diastolic pressure.

Table 2 *Data (mean (SD)) on patients with aortic valve stenosis with or without angina*

Variable	*Patients with angina*	*Patients without angina*	*p*
No of patients	68	15	
Mean age (yr)	66·1 (9·2)	67·5 (8·7)	0·60
Sex ratio (M:F)	56:12	9·6	
Ejection fraction (%)	58 (16)	59 (13)	0·91
LVEDP (mm Hg)	23 (10)	25 (10)	0·55
Gradient (mm Hg)	67 (31)	78 (26)	0·24
Cardiac output (l/min)	5·2* (1·4)	5·1† (1·4)	0·84
Valve area (cm²)	0·69* (0·26)	0·61† (0·17)	0·33
% with significant CAD	66·2	66·7	
% with RWMA	38·2	40·0	

*61 patients, †14 patients.
p values are for two tailed *t* tests.
CAD, coronary artery disease, LVEDP, left ventricular end diastolic pressure, RWMA, regional wall motion abnormalities

Table 3 *Data (mean (SD)) on patients with aortic valve stenosis with or without heart failure*

Variable	*Patients with failure*	*Patients without failure*	*p*
No of patients	26	57	
Mean age (yr)	69·5 (6·7)	64·6 (9·9)	0·03
Sex ratio (M:F)	18:8 (2 25·1)	47.10 (4 7.1)	
Ejection fraction (%)	51 (19)	61 (16)	0·02
LVEDP (mm Hg)	26 (10)	22 (10)	0·17
Gradient (mm Hg)	69 (23)	69 (33)	0·97
Cardiac output (l/min)	4·7* (1·3)	5·3† (1·4)	0·08
Valve area (cm²)	0·61* (0·16)	0·69† (0·28)	0·21
% with significant CAD	58	70	
% with RWMA	42·3	36·8	

*22 patients; †53 patients
p values are for two tailed *t* tests
CAD, coronary artery disease; LVEDP, left ventricular end diastolic pressure; RWMA, regional wall motion abnormality.

Table 4 *Data (mean (SD)) on patients with aortic valve stenosis with or without syncope*

Variable	*Patients with syncope*	*Patients without syncope*	*p*
No of patients	23	60	
Mean age (yr)	65·0 (9·3)	66·6 (9·3)	0·50
Sex ratio (M:F)	15:8	50.10	
Ejection fraction (%)	55 (16)	59 (14)	0·22
LVEDP (mm Hg)	23 (11)	23 (10)	0·93
Gradient (mm Hg)	87 (34)	62 (26)	0·001
Cardiac output (l/min)	5·1* (1·6)	5·2† (1·3)	0·68
Valve area (cm²)	0·58* (0·21)	0·71† (0·25)	0·03
% with significant CAD	61	68·3	
% with RWMA	30	42	

*22 patients, †53 patients.
p values are for two tailed *t* tests
CAD, coronary artery disease; LVEDP, left ventricular end diastolic pressure, RWMA, regional wall motion abnormality.

failure had regional wall motion abnormalities (42·3 *vs* 36·8%). However, six of 26 patients with failure had at least moderately severe diffuse hypokinesia of the left ventricle, while this finding was present in only one of 57 patients who did not have failure. Interestingly, one of the six patients with diffuse hypokinesis had coronary disease. Thus global hypokinesia helped to identify patients with heart failure but regional wall motion abnormalities did not.

Patients with syncope (table 4) had significantly more severe aortic stenosis with higher gradients and lower valve areas than patients without syncope but with equivalent left ventricular systolic function, cardiac outputs, and filling pressures. Coronary artery disease and wall motion abnormalities were more common in patients without syncope. Only four of the 83 patients in the series presented with syncope as their sole symptom, whereas 38 patients had only angina and six had only heart failure. Thirty five patients had two or more of the cardinal symptoms of aortic stenosis.

REGIONAL WALL MOTION ABNORMALITIES

The relation between regional wall motion abnormalities (RWMA) and coronary artery disease (CAD) is shown in the χ^2 2 × 2 table shown below:

	No CAD	*CAD*
RWMA	2	30
No RWMA	26	25

Thirty of 32 patients with regional wall motion abnormality had significant coronary artery disease, whereas 26 of 51 patients with normal wall motion were free of coronary disease. By standard techniques[14] the χ^2 statistic calculated from the data is 15·6. This exceeds the value of 3·84 needed to reject, with a 95% level of certainty, the hypothesis that regional wall motion abnormalities and coronary artery disease are unrelated.

Using Bayesian analysis,[15] one can assess the usefulness of left ventricular regional wall motion abnormality as a screening test for significant coronary artery disease. In this context there were 30 true positives, two false positives, 26 true negatives, and 25 false negatives for a sensitivity of 55%, specificity of 93%, and predictive value of 94%.

Discussion

This study of 83 patients with aortic stenosis and symptoms severe enought to prompt catheterisation before consideration of aortic valve replacement reaffirms the finding that angina pectoris does not predict which of the patients will have significant coronary artery disease. In fact, angina was as common in patients who did not have coronary disease as in those who did. Left ventricular regional wall motion abnormalities predicted the presence of significant coronary artery disease with 94% accuracy. On the other hand, the absence of regional wall motion abnormalities was an insensitive marker of angiographically normal or nearly normal (<50% obstruction of all vessels) coronary arteries, since there was still a 45% chance of significant coronary disease being present. Five of the 83 patients had neither angina nor regional wall motion abnormalities and yet had significant coronary obstruction, so we cannot agree with Graboys and Cohn who believed that the absence of angina virtually excludes coronary disease in patients with aortic stenosis.[1]

Two patients had definite regional wall motion abnormalities but did not have significant coronary disease. Both were women with heart failure, severe aortic stenosis (gradients 109 and 101 mm Hg, valve areas 0·42 and 0·70 cm²), and impaired left ventricular systolic function (ejection fractions of 43 and 33%). Thus it seems that regional wall motion abnormalities occasionally develop, in the absence of coronary obstruction, in the left ventricle that is failing as a result of aortic stenosis; this feature was noted by Milanes *et al* in a recent study of exercise gated nuclear angiography.[16] Diffuse hypokinesis (five patients) is, however, more common.

Although the patients with heart failure had significantly lower cardiac outputs and left ventricular ejection fractions than patients without heart failure, the differences were not pronounced and the values for these two measures of left ventricular systolic function were on average at the lower limits of normal. A previous study by Spann *et al* concluded that contractile function assessed by end systolic pressure relations is impaired in severe aortic stenosis with heart failure, but that cardiac ouput and ejection fraction are maintained at nearly normal values in most cases by increased preload (LVEDP) by the Frank-Starling mechanism,[6] as we also found. On average the left ventricular end diastolic pressures in our patients with heart failure were higher than those in the patients without failure (though they were not statistically significant), despite treatment with digitalis, diuretics, or both in most cases; this further emphasises the role of diastolic dysfunction in the genesis of symptoms in these patients.

Cross sectional echocardiography[17] and radionuclide angiography[16 18] should provide similar sensitivity and specificity for the detection of coronary artery disease via regional wall motion abnormalities as contrast ventriculography in this setting in patients in whom adequate images can be obtained. In addition, echocardiography allows visual, qualitative assessment of the structure and function of all four cardiac valves and quantitative assessment of the transvalvar aortic pressure gradient by Doppler techniques,[19 20] so it would appear to be the ideal technique for non-invasive assessment of patients with aortic stenosis.

There has been considerable controversy over the necessity of routine preoperative coronary angiography in patients with operable valvar heart disease. St John Sutton *et al* have argued that angiography is largely unnecessary[21]; Roberts[22] and O'Rourke[23] disagreed. In our population of mostly elderly patients with symptomatic aortic stenosis, the frequency of significant coronary artery disease was high, and the absence of angina and left ventricular regional wall motion abnormalities was not reliable in excluding significant coronary disease. Therefore, we recommend that coronary angiography be performed before aortic valve replacement for aortic stenosis in adults.

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References

1 Graboys TB, Cohn PF. The prevalence of angina pectoris and abnormal coronary angiograms in severe aortic valvular disease. *Am Heart J* 1977;**93**:683–6.

2 Paquay PA, Anderson G, Diefenthal H, Nordstrom L, Richman HG, Gobel FL. Chest pain as a predictor of coronary artery disease in patients with obstructive aortic valve disease. *Am J Cardiol* 1976;**38**:863–9

3 Swanton RH, Brooksby IAB, Jenkins BS, *et al.* Determinants of angina in aortic stenosis and the importance of coronary arteriography. *Br Heart J* 1977;**39**:1347–52.

4 Gunther S, Grossman W. Determinants of ventricular function in pressure-overload hypertrophy in man. *Circulation* 1979;**59**:679–88.

5 Huber D, Grimm J, Koch R, Krayenbuehl HP. Determinants of ejection performance in aortic stenosis. *Circulation* 1981;**64**:126–34.

6 Spann JF, Bove AA, Natarajan G, Kreulen T. Ventricular performance, pump function, and compensatory mechanisms in patients with aortic stenosis. *Circulation* 1980;**62**:576–82.

7 Copeland JL, Griepp RB, Stinson EB, Shumway NE. Long-term follow-up after isolated aortic valve replacement. *J Thorac Cardiovasc Surg* 1977;**6**:875–85.

8 Storstein O, Enge I. Angina pectoris in aortic valvular disease and its relation to coronary pathology. *Acta Med Scand* 1979;**205**·275–8.

9 Liedtke AJ, Gentzler RD, Babb JD, Hunter AS, Gault JH. Determinants of cardiac performance in severe aortic stenosis. *Chest* 1976;**69**:192–200.

10 St John Sutton MG, Tajik AJ, Smith HC, Ritman EL Angina in idiopathic hypertrophic subaortic stenosis. A clinical correlate of regional left ventricular dysfunction: a videometric and echocardiographic study *Circulation* 1980;**61**:561–8.

11 Osbakken MD, Bove AA, Spann JF Left ventricular regional wall motion and velocity of shortening in chronic mitral and aortic regurgitation. *Am J Cardiol* 1981;**47**.1005–9.

12 Hakki A-H, Iskandrian AS, Bemis CE, *et al.* A simplified valve formula for the calculation of stenotic cardiac valve areas. *Circulation* 1981,**63**.1050–5

13 Wexler LF, Lesperance J, Ryan TJ, *et al.* Interobserver variability in interpreting contrast left ventriculograms (CASS). *Cathet Cardiovasc Diagn* 1982; **8**·341–55

14 Spiegel MR. *Statistics.* New York: Schaum, 1961. 188–91.

15 Braunwald E, ed. *Heart disease.* Philadelphia: WB Saunders, 1980:270.

16 Milanes JC, Paldi J, Romero M, Goodwin D, Hultgren HN. Detection of coronary artery disease in aortic stenosis by exercise gated nuclear angiography. *Am J Cardiol* 1984;**54**.787–91.

17 Weyman AE. *Cross-sectional echocardiography.* Philadelphia: Lea and Febiger, 1982:304–24.

18 Berger HJ, Zaret BL. Nuclear cardiology (Part II). *N Engl J Med* 1981;**305**:855–65.

19 Currie PJ, Seward JB, Reeder GS, *et al.* Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients *Circulation* 1985;**71**:1162–9.

20 Callahan MJ, Su-Fan Q, Tajik AJ, Bove AA. Validation of instantaneous pressure gradients measured by continuous-wave Doppler in experimentally induced aortic stenosis. *Am J Cardiol* 1985;**56**:989–93.

21 St John Sutton MG, St John Sutton M, Oldershaw P, *et al.* Value replacement without preoperative cardiac catheterization. *N Engl J Med* 1981,**305**:1233–8.

22 Roberts WC. Reasons for cardiac catheterization before cardiac valve replacement. *N Engl J Med* 1982; **306**:1291–3.

23 O'Rourke RA. Preoperative cardiac catheterization: its need in most patients with valvular heart disease. *JAMA* 1982;**248**:745–50.

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Radionuclide left ventricular ejection fraction: a comparison of three methods

ANGAS D B HAINS, IMAD AL-KHAWAJA, DAVID A HINGE, AVIJIT LAHIRI, EDWARD B RAFTERY

From the Department of Cardiology and the Division of Clinical Sciences, Northwick Park Hospital and Clinical Research Centre, Watford Road, Harrow, Middlesex

SUMMARY Three commercially available computer programs (a semiautomatic method, a manual method, and a regional method) were used to calculate left ventricular ejection fraction from the equilibrium multiple gated radionuclide ventriculograms obtained from 24 normal male subjects and 20 men with heart failure. In the normal subjects the ejection fraction values calculated by each method were significantly different (mean (SD) difference between semiautomatic and manual 3·3 (5 8); between semiautomatic and regional 12·0 (6·3); and between manual and regional 8·7 (6·9)). In the patients with heart failure the ejection fraction values calculated by the semiautomatic method differed significantly from those calculated by the manual and regional methods (mean (SD) difference between semiautomatic and manual 3·4 (4·7); between semiautomatic and regional 4·9 (4·9); and between manual and regional 1·5 (6·2)). The ejection fraction values obtained by the semiautomatic method were generally higher and more consistent than those derived from the manual and regional methods. An ejection fraction of ≥50% with the semiautomatic method would be regarded as normal but if the same normal range was applied to the regional method nine (38%) of the 24 normal subjects would appear to have an abnormal left ventricular function.

Clinicians should be aware that the method used to generate a time-activity curve is an important consideration in the calculation of ejection fraction. Each centre should establish its own range and reproducibility for the method it uses to measure ejection fraction. These values should not be assumed to apply to any other method.

Since the first descriptions of the use of radionuclide techniques to measure left ventricular ejection fraction[1 2] and to detect regional ventricular dysfunction,[3] radionuclide ventriculography has become increasingly important not only to the management of patients with cardiac disease but also to the investigation of patients in various physiological states and during pharmacological intervention. The technique is safe, repeatable, and does not induce measurable alterations in haemodynamic function.[4] Initially, manual methods were used to calculate the ejection fraction from the radionuclide scan with the observer tracing the ventricular margin in end diastole and end systole; many centres still use this method. Improved computer technology has produced automated techniques for tracing the ventricular contour, these techniques relying on edge defining algorithms to detect the ventricular margin. Automated techniques are claimed to give more consistent results[5]; however, some believe that edge defining algorithms are liable to error and they still favour the manual method for selecting regions of interest.[6] Automation has increased the number of companies marketing programs and the number of programs available to calculate ejection fraction. These programs differ in the way in which they generate a time-activity curve and it is apparent that this may lead to differences in ejection fraction values between programs.

The purpose of this study was to investigate the differences between three commercially available

Requests for reprints to Dr Edward B Raftery, Northwick Park Hospital and Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ

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methods used to calculate ventricular ejection fraction and to assess the variability of these methods.

Patients and methods

The multiple gated radionuclide ventriculograms of 24 normal men and 20 men with heart failure were studied retrospectively. All the normal subjects had no history of cardiac disease, normal cardiovascular examination, and a normal electrocardiogram. Ischaemic heart disease was the cause of heart failure in 18 patients, with alcoholic cardiomyopathy and cardiomyopathy of unknown cause being the primary diagnoses in the other two patients.

Red blood cells were labelled in vivo by an intravenous injection of 10 mg unlabelled stannous pyrophosphate followed 20 minutes later by 740 mBq of technetium-99m. Multiple gated ventriculograms were obtained by means of an Anger scintillation camera with a low energy, all purpose collimator (Elscint, Apex 215M). The camera was positioned in the 30°–45° left anterior oblique projection with 5°–10° caudal tilt in order to isolate the left ventricle. The R-R interval was divided into 32 frames and a 5% gate tolerance was used. Five million counts were collected and the data were stored on a 64 × 64 matrix to obtain a high resolution time-activity curve of the change in precordial radioactivity.

Three commercially available programs that are widely used in different centres were used to measure the left ventricular ejection fraction from the ventriculogram—a semiautomatic method,[7] a manual method, and a regional method[8] that estimates the ejection fraction of the lateral, inferoapical, and septal regions as well as the global ejection fraction. The same time correction and nine point smoothing was applied to every scan studied by each method. To correct for non-cardiac activity the same background region of interest was used with each method; this region was two pixels wide and two pixels from the left lower quadrant of the left ventricle on the end systolic frame. The method used to generate a time-activity curve was different with each program. With the semiautomatic method the observer drew a region of interest around the ventricle on the first frame. A second derivative edge-defining algorithm automatically determined the ventricular outline of all frames of the cycle. If necessary the observer could alter the outline of any frame. With the manual method the observer traced the outline of the ventricle on the first frame and the end systolic frame. With the regional method the observer drew a region of interest around the ventricle on the first frame and a second derivative edge-defining algorithm was used to determine the ventricular outline in this frame, the outline being altered by the observer if necessary. This outline was then positioned on all 32 frames.

One observer (observer 1) estimated the ejection fraction in all subjects using each program on two separate occasions. The intraobserver variability was estimated from the results of the 24 normal subjects only. The mean of the two ejection fraction readings was used to analyse the differences between the programs. Two other observers (observers 2 and 3) estimated the ejection fraction in 10 of the 24 normal subjects using each program on one occasion. Their results were compared with the first estimation by observer 1 in the same 10 subjects to estimate the interobserver variability for each program.

Student's *t* tests (two tailed) were used to estimate the intraobserver variability. Two way analysis of variance was used to estimate the interobserver variability and the differences between the three programs. A difference was regarded as significant when $p < 0.05$.

Results

The mean age of the 24 normal subjects was 37 years (range 20–58) and that of the 20 patients with heart failure was 61 years (range 47–74). The mean ejection fraction (SD) in the 24 normal subjects was 63 (6·9)% (range 51–78%) for the semiautomatic method, 60 (6·3)% (range 46–70%) for the manual method, and 51 (8·2)% (range 35–66%) for the regional method. In the 20 patients with heart failure the mean ejection fractions were 29 (9·4)% (range 14–45%), 26 (9·4)% (range 13–46%), and 24 (5·9)% (range 17–38%) for semiautomatic, manual, and regional methods respectively.

INTRAOBSERVER AND INTEROBSERVER VARIABILITY

A comparison of the first and second ejection fraction values obtained by each method in both groups (table 1) showed no significant intraobserver variability in either group with any of the methods. The comparison of the readings obtained by three observers using each method in 10 of the 24 normal subjects (tables 2 and 3) showed no significant interobserver variability. Comparison of the intraobserver and interobserver variability in the normal subjects (table 4), however, showed that the interobserver variability was significantly greater than the intraobserver variability with the manual and regional methods ($p < 0.05$ and $p < 0.025$ respectively) but not with the semiautomatic method (p = NS).

COMPARISON OF PROGRAMS

We compared the three programs in both groups of

Table 1 *Comparison of the first and second ejection fraction (EF) values obtained by each method in the normal subjects and subjects with heart failure*

Method used to measure EF	*Mean difference*	*SE of mean difference*	*p value*
Normal.			
Semiautomatic	−0·29	0·61	NS
Manual	−0·13	0·75	NS
Regional	+0·88	0·76	NS
Heart failure			
Semiautomatic	+0·20	0·50	NS
Manual	+1·40	0·80	NS
Regional	−0·60	0·61	NS

Table 2 *Comparison of ejection fraction (EF) values obtained by observers 1 and 2 in 10 normal subjects*

Method used to measure EF	*Mean difference*	*SE of mean difference*	*p value*
Semiautomatic	−1·2	1·16	NS
Manual	−2·0	2·01	NS
Regional	−2·4	1·96	NS

Table 3 *Comparison of ejection fraction (EF) values obtained by observers 1 and 3 in 10 normal subjects*

Method used to measure EF	*Mean difference*	*SE of mean difference*	*p value*
Semiautomatic	−1·8	1·31	NS
Manual	−0·9	1·35	NS
Regional	−1·8	2·11	NS

subjects by plotting the average of the mean ejection fraction obtained by any two programs against their difference.[9] In the normal subjects (fig 1) the mean difference (SD) between the semiautomatic and manual methods was 3·3 (5·8)% (p < 0·02), between the semiautomatic and regional methods it was 12·0 (6·3)% (p < 0·0001), and between the manual and regional methods it was 8·7 (6·9)% (p < 0·0001). There was no correlation between the average ejection fraction and the difference for any of the comparisons, indicating that the difference was not related to the magnitude of the ejection fraction. As shown on the histograms of the distribution of differences, the ejection fractions obtained from the semiautomatic method were generally higher than those from the other two methods; the ejection fractions obtained from the regional method were appreciably lower than the semiautomatic and manual methods. In the patients with heart failure (fig 2) the mean (SD) difference between the semiautomatic and manual methods was 3·4 (4·7) (p < 0·01), between the semiautomatic and regional methods it was 4·9 (4·9) (p < 0·0005), and between the manual and regional methods it was 1·5 (6·2) (p = NS). There was no correlation between the average ejection fraction and the difference when the semiautomatic and manual methods were compared but there was a positive correlation for the comparison of semiautomatic and regional methods (r = 0·75, p < 0·0002) and manual and regional methods (r = 0·60, p < 0·005). Again the ejection fraction values obtained with the semiautomatic method were generally higher than those obtained with the manual and regional methods.

Discussion

We have compared three commercially available programs that are used for the estimation of ejection fraction and we have demonstrated that the method used to generate a time-activity curve is an important consideration in the calculation of ejection fraction. Throughout the whole range of ejection fraction values the semiautomatic method gave significantly higher values than the manual and regional methods. The semiautomatic method also produced more consistent results than the other two methods with which the interobserver variability was significantly greater than the intraobserver variability. However, our results with the manual method do not support the view of Reiber *et al* that the manual method is characterised by large interobserver and intraobserver variations.[5]

There are important differences between the three programs in the method of generating a time-activity curve. With the manual method the first frame is assumed to be the end diastolic frame. The end diastolic frame is sometimes at a different point in the cycle, however, and this would lead to an underestimation of the end diastolic counts and,

Table 4 *Comparison of intraobserver and interobserver variability in ejection fraction in normal subjects*

Method used to measure EF	*SD of differences between 2 EF values obtained by observer 1 (SD_1)*	*SD of differences in EF values obtained by 3 observers (SD_2)*	*Ratio of variance (SD_2^2/SD_1^2)*	*p value*
Semiautomatic	3·00	3·71	1·53	NS
Manual	3·69	5·51	2·23	<0·05
Regional	3·71	6·21	2·80	<0·025

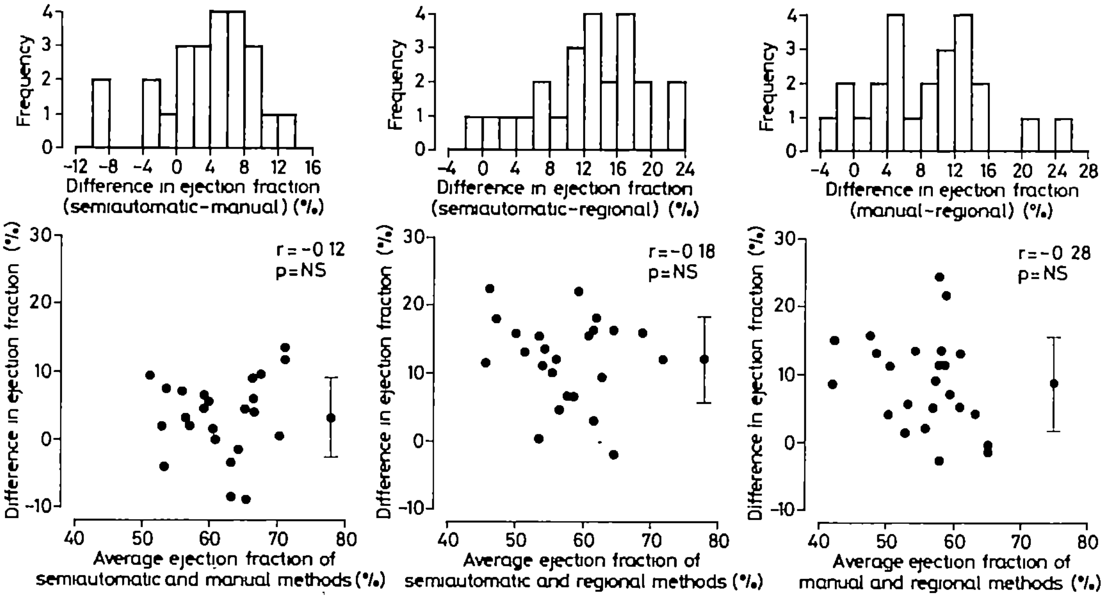

Fig 1 *Comparisons of the mean ejection fraction values obtained with each method in 24 normal subjects The mean difference ±1 SD is shown for each comparison*

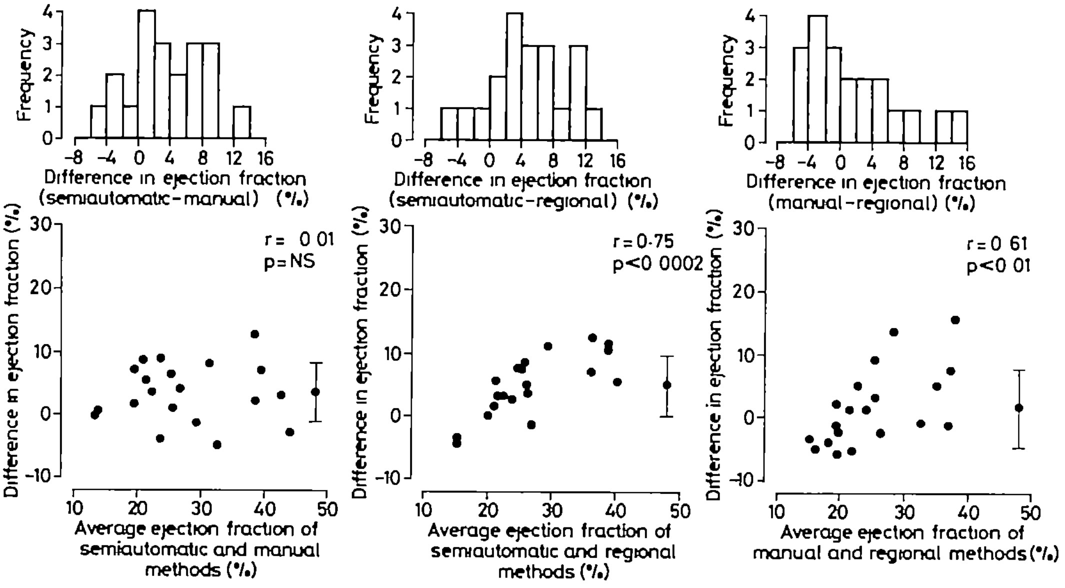

Fig 2 *Comparisons of the mean ejection fraction values obtained with each method in 20 patients with heart failure. The mean difference ±1 SD is shown for each comparison.*

therefore, of the ejection fraction. Because the semiautomatic method defines the ventricular margin in all 32 frames it identifies the end diastolic frame more accurately. We believe that this difference in identifying the end diastolic frame accounts for the differences observed between these two methods. The regional method used transfers the left ventricular margin from the first frame on to all the frames in the cycle. Again the assumption that the first frame is the end diastolic frame could lead to an underestimation of the ejection fraction. Furthermore, by superimposing the left ventricular margin from the first frame on to all frames the counts from the end systolic frame will include extracardiac counts and this will lead to further underestimation of the ejection fraction. At low ejection fractions the effect of the extracardiac counts will be less because the end diastolic left ventricular margin will approximate the end systolic left ventricular margin; as the ejection fraction increases the extracardiac counts increase and this approximation becomes less. It is this factor that accounts for the positive correlation between the average ejection fractions and the differences between methods when the regional method is compared with the semiautomatic and manual methods in the patients with heart failure. In our centre the normal range of ejection fraction established with the semiautomatic methods was $\geqslant 50\%$. If this normal range was applied to the regional method nine (38%) of the 24 normal subjects would be regarded as having abnormal cardiac function.

Although the semiautomatic method produces the most consistent results it is difficult to prove that it produces the most accurate results. Cardiac phantoms have been used to determine the most accurate methods but there are large differences between the quoted and estimated ejection fraction.[6] The verification of programs remains a problem; until it is solved unsatisfactory programs will continue to be marketed and comparison between different centres will remain difficult. Because the time-activity curve is now being used to calculate various indices of ventricular systolic and diastolic function the issue of quality control becomes even more important. It has been suggested that quality control of the analysis software is best done by means of a library of patient data, the results of which have been previously authenticated.[6] However, as was acknowledged, if the data were collected on another system the problem of data transfer and compatibility becomes a major issue.

Clinicians should be aware that the measurement of ejection fraction is dependent on the method used and each centre should establish its own normal range and reproducibility for the method it uses to measure the ejection fraction and should not assume that these values will apply to any other method or even to the same method produced by another company.

We wish to acknowledge the assistance of Caroline Dore, Department of Statistics, and Dr John Whittington, Department of Cardiology.

References

1 Strauss HW, Zaret BL, Hurley PJ, Natarajan TK, Pitt B. A scintiphotographic method for measuring left ventricular ejection fraction in man without cardiac catheterisation. *Am J Cardiol* 1971;**28**:575–80.

2 Parker JA, Secker-Walker R, Hill R, Siegel BA, Potchen EJ. A new technique for the calculation of left ventricular ejection fraction. *J Nucl Med* 1972; 13.649–51.

3 Zaret BL, Strauss HW, Hurley PJ, Natarajan TK, Pitt B. A noninvasive scintiphotographic method for detecting regional ventricular dysfunction in man. *N Engl J Med* 1971;**284**.1165–70.

4 Ashburn WL, Schelbert HR, Verba JW Left ventricular ejection fraction—a review of several radionuclide angiographic approaches using the scintillation camera. *Prog Cardiovasc Dis* 1978;**20**:267–84.

5 Reiber JHC, Lie SP, Simmons ML, *et al* Clinical validation of fully automated computation of ejection fraction from gated equilibrium blood-pool scintigrams. *J Nucl Med* 1983;**24**:1099–107.

6 Cradduck TD, Busemann-Sokole E Dependence of ejection fraction results on choice of algorithms for a cardiac phantom. *Nuc Med Commun* 1986;7·33–44.

7 Pfisterer ME, Battler A, Swanson SM, Slutsky R, Froelicher V, Ashburn WL Reproducibility of ejection-fraction determinations by equilibrium radionuclide angiography in response to supine bicycle exercise· concise communication. *J Nucl Med* 1979;**20**·491–5.

8 Maddox DE, Wynne J, Uren R, *et al.* Regional ejection fraction. a quantitative radionuclide index of regional left ventricular performance. *Circulation* 1979;**59**: 1001–9

9 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**i**:307–10.

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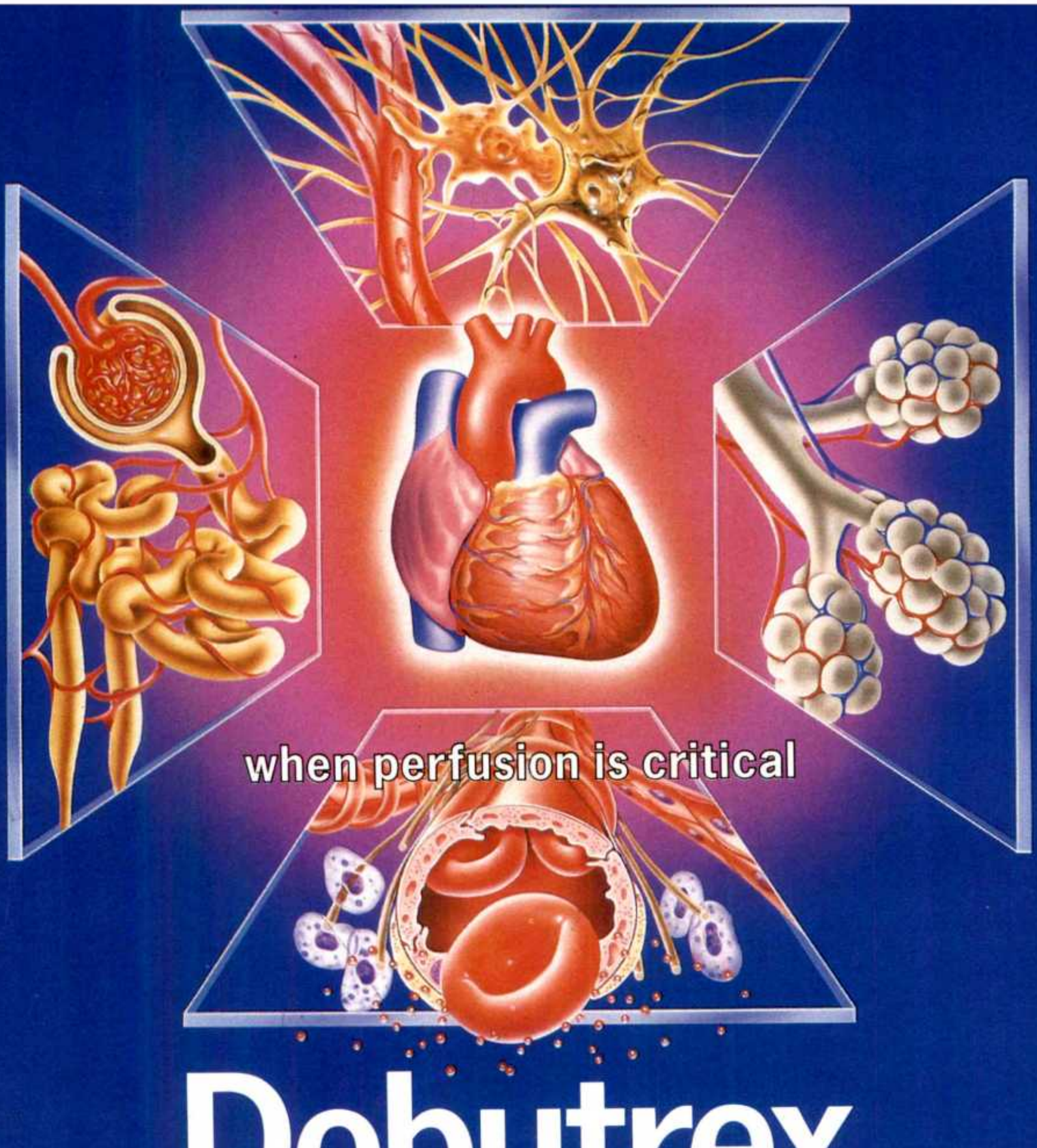

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"Syndrome myxoma": a subset of patients with cardiac myxoma associated with pigmented skin lesions and peripheral and endocrine neoplasms

HUMBERTO J VIDAILLET JR, JAMES B SEWARD, F EARL FYKE III, W P DANIEL SU, A JAMIL TAJIK

From the Department of Internal Medicine and the Department of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

SUMMARY From January 1954 to December 1985 cardiac myxoma was diagnosed in 75 patients at the Mayo Clinic. The clinical presentation was typical in 70 cases and was referred to as "sporadic myxoma". Forty four other cases of cardiac myxomas (five from the Mayo Clinic) presented with a combination of distinctive clinical features and these cases are described as "syndrome myxoma". The patients with syndrome myxoma were younger (mean age, 25 *vs* 56 years) and had unusual skin freckling (68%), associated benign non-cardiac myxomatous tumours (57%), endocrine neoplasms (30%), and a high frequency of familial cardiac myxoma (25%) and familial endocrine tumours (14%). The two types of cardiac tumour were different (syndrome *vs* sporadic): atrial location, 87% *vs* 100%; ventricular location, 13% *vs* 0%; single tumour, 50% *vs* 99%; multiple tumours, 50% *vs* 1%; and recurrent tumour, 18% *vs* 0%.

It is concluded that patients with syndrome myxoma represent a distinctive subgroup in which there are important clinical, surgical, and genetic implications. More importantly, syndrome myxoma appears to be only one expression of a much larger disease entity.

Although it is rare, cardiac myxoma is the most frequently encountered primary neoplasm of the heart.[1] Cardiac myxomas are typically sporadic, benign, non-recurring, left atrial tumours.[1] They are usually attached to the atrial septum, in or about the valve of the fossa ovalis, and are more common in females and in patients aged from 30 to 60.[2]

From a review of experience at the Mayo Clinic and a critical review of published reports we recognised a subset of patients with cardiac myxoma and associated systemic manifestations including pigmented skin lesions and non-cardiac tumours.[3] These patients have distinctive clinical features that separate them from the larger group of patients with the more common sporadic myxoma.[2] We call the condition in this subset of patients "syndrome myxoma".

We have compared sporadic myxoma with syndrome myxoma and we summarise the specific findings that allow clinical distinction between the two. The most important distinction is that syndrome myxoma appears to be a multisystem disease.

Patients and methods

From 1954 to 1985, 75 patients with cardiac myxoma were seen at the Mayo Clinic. Seventy of them had the sporadic type of cardiac myxoma. Five (7%) patients have subsequently been recognised as having an atypical presentation and these were the original cases that prompted the use of the term syndrome myxoma. We defined syndrome myxoma as cardiac myxoma with one or more of the following features: cutaneous lentiginosis or unusual hyperpigmented skin lesions (that is, unusual or excessive freckling), non-cardiac myxoid tumours or neurofibromas, or a rare endocrine neoplasm. When we used these three criteria to review published reports we found 39 additional cases of syndrome

Requests for reprints to Dr James B Seward, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

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Table 1 *Details of 44 patients with syndrome myxoma*

Case No	*Reference*	*Age (yr)*	*Sex*	*Cardiac myxoma*	*Pigmented macules*	*Non-cardiac myxoma*	*Other*	*Familial feature*	*Clinical features*
1	4	16	M	LA and LV (S)	+	—	—	–	Blue naevi (multiple)
2	5	10	M	Biatrial (S)	+	Sk (NF)	AH	–	Blue naevi
3	6	29	M	LA and RV (S)	–	Sk	—	–	Hurthle cell thyroid adenoma
4	7	26	F	4 in RA (S)	–	Sk, Br, U	AH, pheo	+	Sister of case 5
5	7	?	F	Site unknown	+	Sk, Br	AH	+	
6	8	16	M	RV	–	Sk	LCCSC	–	
7	9	12	F	RA	–	Br	AH	+	Mother had LA myxoma
8	10	29	F	Biatrial (S)	+	—	—	–	
9	11	22	F	Biatrial (S)	+	—	—	–	
10	12	16	F	LA	+	Sk, Br	—	+	Four myxoma operations (see fig 3)
		18		LA (R) (multiple)					
		20		RA and LA (R) (multiple)					
		29		RA (R)					
11	12	56	M	LA	+	Sk	—	+	Father of case 10 (see fig 3)
12	13	14	F	Biatrial (S)	+	—	—	–	
13	14	45	F	RA, LA, RV, LV (S)	–	Sk	AH	–	
14	15	46	M	LA (2 stalks)	–	Sk	—	+	Possible acromegaly
		46		4 LA					
		52		6 LA					
				RA					
15	16	23	M	RV	–	Sk	LCCSC	+	Identical twin with RV myxoma
16	17	?	F	Site unknown	–	—	AH	–	
17	18	12	F	2 LA (S)	+	—	—	–	Hispanic
18	19	25	F	RA	–	Sk, Br	—	+	
19	20	24	F	LA, LV (S)	+	Sk, Br	—	+	Brother with acromegaly, cardiac myxoma, lentigines
20	21	18	M	LA	–	Sk	—	–	3 myxoma operations
21	22	19	M	RA	+	—	—	–	
22	23	14	M	LA	+	—	—	–	
23	24	26	M	RV	+	—	Test. tumour	–	
24	25	16	M	LV	+	—	AH, LCCSC	+	Brother of case 25
25	25	10	M	LA	+	—	AH, LCCSC	+	Brother of case 24
26	26	?	F	Site unknown	–	—	Acromegaly	–	
27	27	18	M	LA	+	Palate NF	—	–	2 myxoma operations
		?	M	LV (R)					
28	28	10	F	RA	+	Sk, Br, vulva	—	–	Blue naevi
29	28	?	F	Site unknown	+	—	—	+	
30	28	?	M	Site unknown	+	—	—	+	
31	28	?	F	Site unknown	+	—	—	+	
32	29	33	F	LA	–	Br, FA	—	–	2 myxoma operations
	30	39		LA (R)					
33	29	37	F	LA	–	Br, FA	—	–	
34	31	36	F	LA	+	Br, FA, Sk	AH	+	Brother with LA myxom
35	32	25	F	RA, 2 LA (S)	–	Palate NF	—	+	Hispanic, sister with LA myxoma
36	33	30	F	RV	+	Br, vulva, NF	—	–	
37	34	15	F	RA, 2 LA (S)	+	Sk	—	–	
38	PC	12	F	Biatrial (S)	+	—	—	–	Hispanic
39	PC	37	F	LV	+	—	—	–	Multiple naevi
40	Mayo	17	F	Biatrial (S)	+	Sk	—	–	2 myxoma operations
		19		RA (R)		Sk	—	–	
41	Mayo	32	F	3 RA (S)	+	Br, FA	—	–	3 myxoma operations (see fig 4)
		35		4 LA (S)					
		45		LA (R)					
42	Mayo	33	F	LA	+	—	—		
43	Mayo	52	M	LA	+	Vocal cord	—	–	
44	Mayo	33	F	RA	+	Sk	—	–	2 myxoma operations
		43		2 RA, LA (R) (S)					

AH, adrenal hyperplasia; Br, breast; FA, fibroadenoma; LA, left atrium; LCCSC, large cell calcifying Sertoli cell testicular tumour; LV, left ventricl NF, neurofibroma; PC, personal communication; pheo, pheochromocytoma; R, recurrence; RA, right atrium; RV, right ventricle; S, synchronous; Sk, ski Test., testicular; U, uterus; V, ventricle; ?, not known.

myxoma. Each example was originally reported as an isolated case. We compared the 44 cases of syndrome myxoma with the 70 cases of sporadic cardiac myxoma at the Mayo Clinic.

Results

SYNDROME MYXOMA PATIENTS

Table 1 shows data on the 44 patients with syndrome

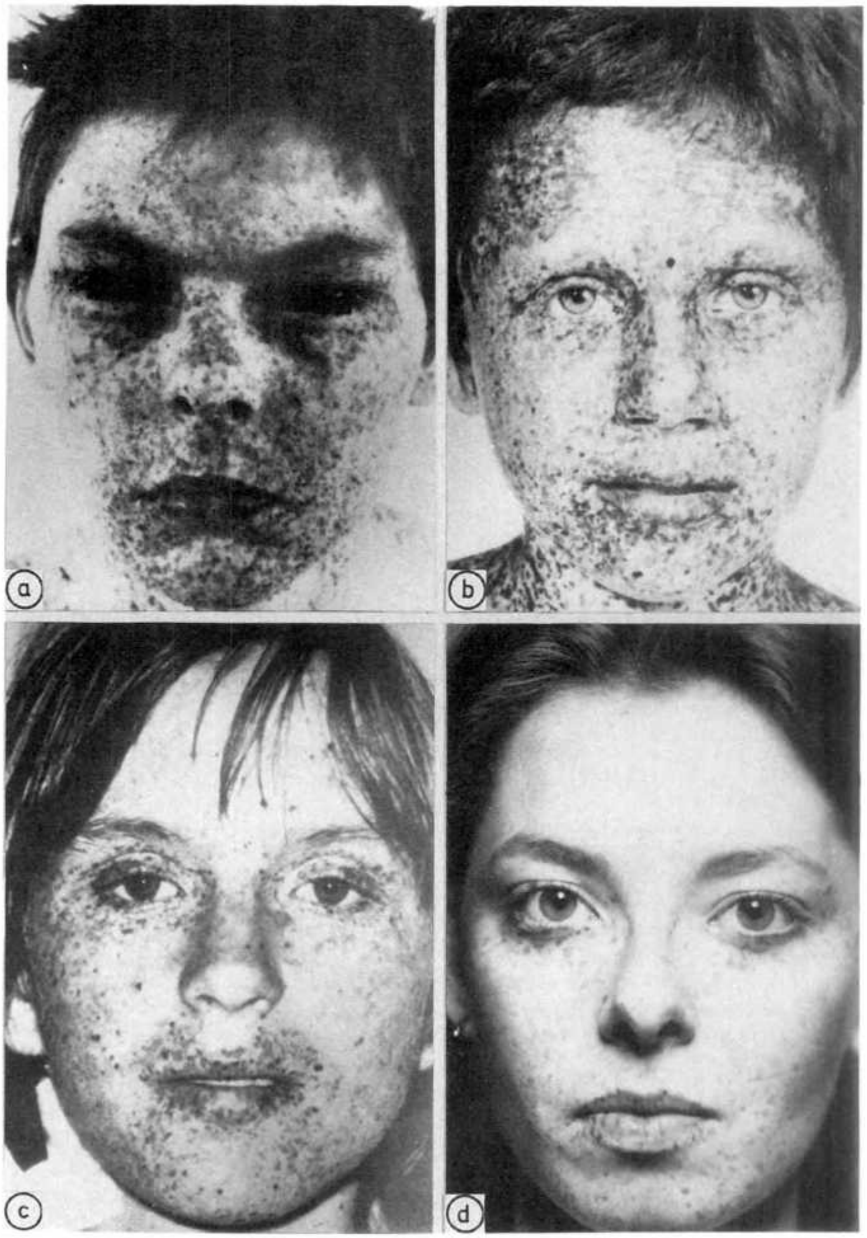

Fig 1 *Unusual facial freckling in four patients with atrial myxoma. (a) Eighteen year old man (case 27) with extensive freckling, palatal myxoid neurofibroma, and reddish hair. (From Rees et al.*[27] *By permission of the British Heart Journal.) (b) Ten year old boy (case 4) with biatrial myxoma, freckling, skin myxoid neurofibromas, blue naevi, and rust red hair. (From Atherton et al.*[5] *By permission of the British Association of Dermatologists.) (c) Fourteen year old boy (case 23) with left atrial myxoma, lentigines, and red hair. (From Peterson and Serrill*[23]*; by permission of the American Academy of Dermatology, Inc.) (d) Seventeen year old girl (case 40) with biatrial myxoma; right atrial myxoma recurred at age 19. There were extensive freckling and skin myxomas.*

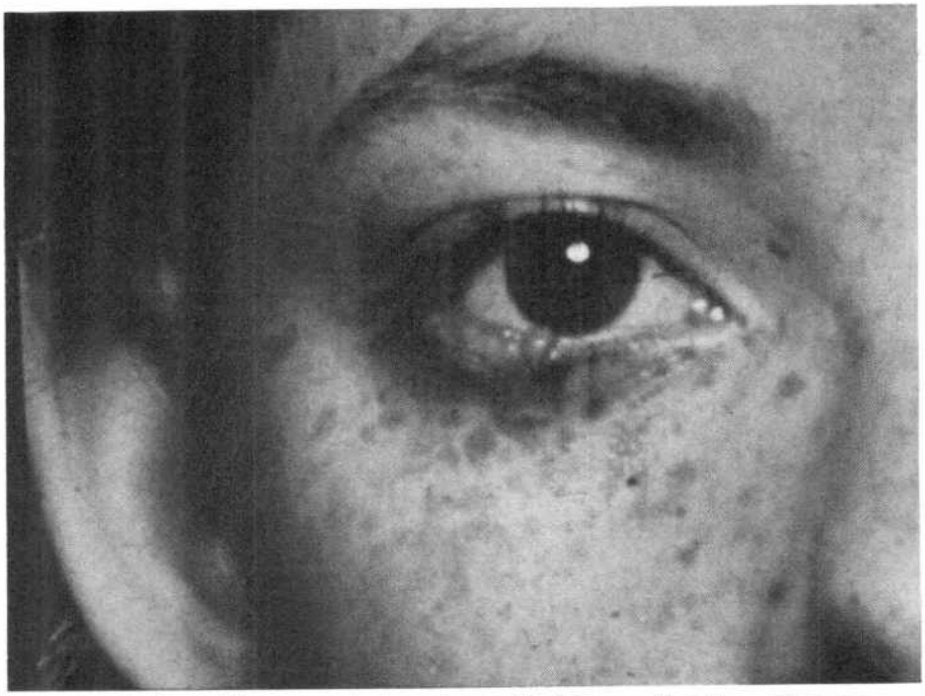

Fig 2 *Peripheral myxoid tumour on the lower right eyelid of 17 year old girl (case 40) (same patient as in fig 1 d).*

myxoma. Patients with syndrome myxoma were significantly younger (mean age 25 years) and had a high frequency of non-cardiac manifestations: freckling (30 patients, 68%), peripheral tumours (25 patients, 57%), or endocrine neoplasms (13 patients, 30%). Half of these 44 patients had one associated feature, 19 (43%) had two, and three (7%) had all three. There were 28 women and 16 men (ratio, 1·8:1).

Cardiac myxoma

The 44 patients had a total of 103 cardiac myxomas (2·3 myxomas per patient). Half of them had multiple cardiac myxomas and half had a single cardiac myxoma. In patients with single tumours, 41% were in the left atrium, 24% were in the right atrium, and 35% were in the ventricles. Twelve (27%) of the 44 patients had at least one ventricular myxoma.

Fifty two (50%) of the 103 tumours were in the left atrium, 32 (31%) were in the right atrium (10 were synchronous biatrial), 13 (13%) were ventricular (7 right and 6 left), and in six the affected chamber was unknown. Eight (18%) of the 44 patients had at least one recurrence of a cardiac myxoma and three had a third operation for recurrence (cases 10, 20, 41).

Pigmented skin lesions

Thirty (68%) of the 44 syndrome myxoma patients had unusual facial and truncal "freckling" (fig 1). Published reports described patients as having simple freckles, lentigenes, multiple superficial naevi, "cutaneous pigmented macules," and blue naevi. Several patients had both lentigenes and freckles. Each type of cutaneous lesion was confirmed by skin biopsy. At least four of the patients had hyperpigmented macules of the mucous membranes. The freckling is usually described as centrofacial rather than peripheral.

Peripheral tumours

Peripheral myxoid tumours (fig 2) or neurofibromas were present in 25 (57%) of the 44 patients; the sites included the breasts, face, extremities, torso, vulva, uterus, buttocks, and vocal cords. Two patients (cases 27 and 35) had neurofibromas of the palate. Histologically these tumours were myxomas, myxoid fibroadenomas, myxoid neurofibromas, neurofibromas, and myxoid leiomyomas. Several

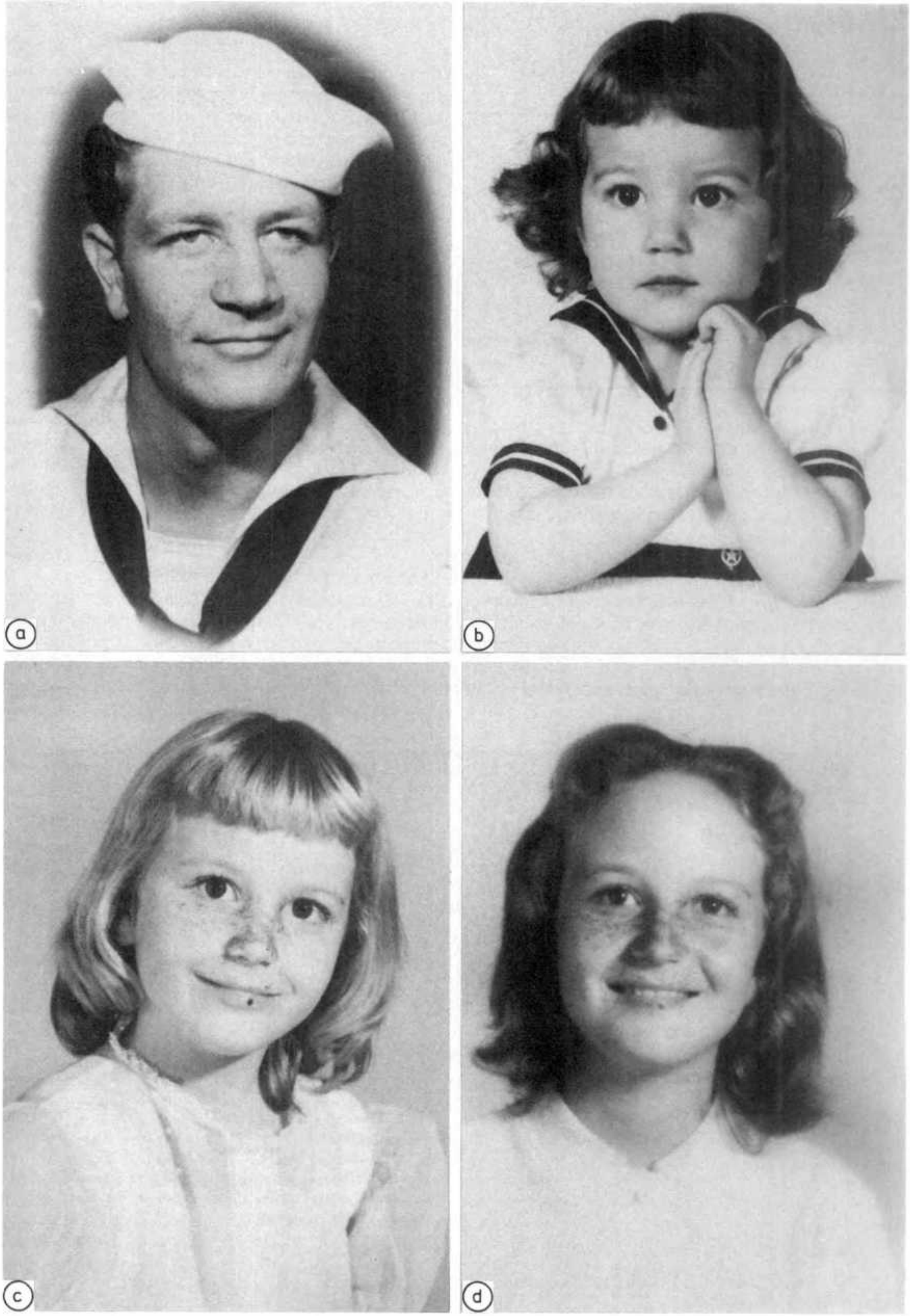

Fig 3 *(a) The father is pictured in his twenties; diffuse lentiginoses were present. He died at age 56 from a left atrial myxoma. His daughter (b, c, d) pictured at ages 2, 7, and 13 years, had diffuse lentiginoses that were apparent at a very early age and became more apparent with age. She died aged 21 after four operations for cardiac myxomas.*

Table 2 *Comparison of clinical features of sporadic myxoma and syndrome myxoma*

Feature	*Sporadic*	*Syndrome*
Age (yr) (range)	56 (39–82)	25 (10–56)
Female/male ratio	2·7:1	1·8:1
Patients (No)	70	44
Cardiac myxomas (No)	72	103
Distributions of myxomas (%):		
Atrial/ventricular	100/0	87/13
Single/multiple	99/1	50/50
Biatrial	0	23
Recurrent	0	18
Familial	0	27
Freckling (%)	0	68
Non-cardiac tumours (%)	0	57
Endocrine neoplasm (%)	0	30
Familial (%)	0	14

patients had both myxoid cutaneous tumours and myxoid fibroadenomas of the breast. Most patients had only one histological type of tumour. None of these patients had von Recklinghausen's neurofibromatosis or Albright's syndrome.

Endocrine neoplasms

Thirteen (30%) patients had associated endocrine tumours. Three patients had multiple endocrine neoplasms. The adrenal cortex was affected in eight patients; several of these had clinical Cushing's syndrome requiring bilateral adrenalectomy, and one of these also had a pheochromocytoma. Testicular tumours were present in five patients (four with large cell calcifying Sertoli cell testicular tumours and one with an interstitial cell tumour of the testis producing androstanedione and testosterone). Only testicular, adrenal, or pituitary tumours were regarded as valid for entry criteria; however, many patients had thyroid neoplasms, including Hürthle cell adenoma of the thyroid, mixed papillary and follicular epithelial hyperplasia, and thyroid carcinoma. None of these patients had a recognisable multiple endocrine adenomatosis syndrome, neurofibromatosis, or Albright's syndrome.

Familial features

In addition to the freckling (fig 3) seen in many of the first degree relatives of syndrome myxoma patients, 15 (34%) patients had at least one of the following: familial cardiac myxoma, 11 patients; familial non-cardiac myxoid tumours, eight patients; familial endocrine neoplasms, six patients; two or three familial features, eight patients.

SPORADIC CARDIAC MYXOMA

The 70 consecutive patients from a single institution had a total of 72 myxomas (approximately one myxoma per patient) and the clinical presentations and associations were distinctly different from those in patients with syndrome myxoma (table 2). Most of

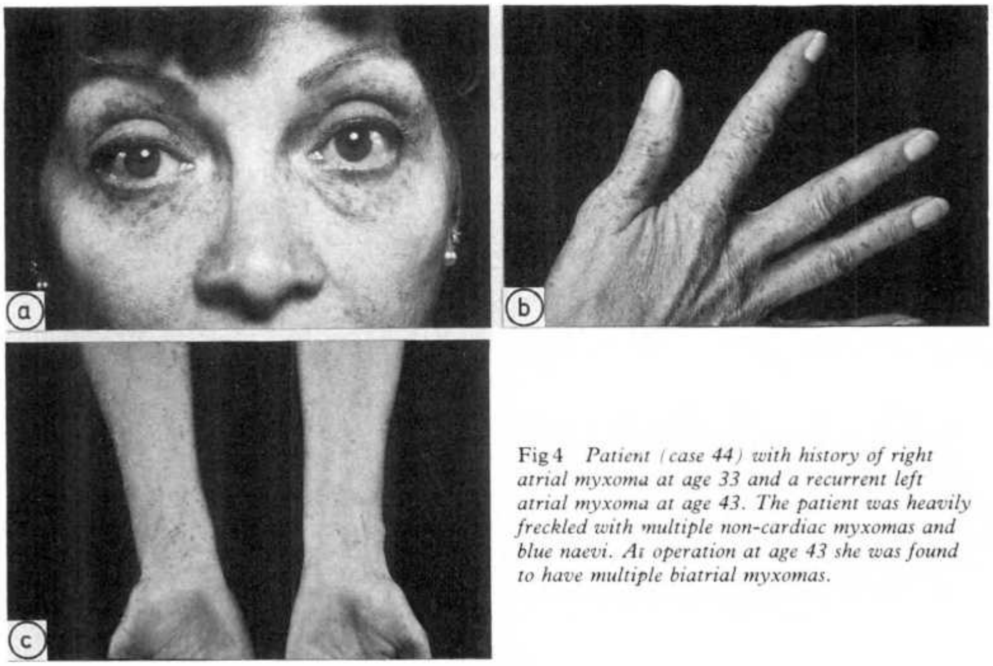

Fig 4 *Patient (case 44) with history of right atrial myxoma at age 33 and a recurrent left atrial myxoma at age 43. The patient was heavily freckled with multiple non-cardiac myxomas and blue naevi. At operation at age 43 she was found to have multiple biatrial myxomas.*

these patients have been reported elsewhere.[35-37] There were no bilateral or ventricular myxomas. There were no recurrences and no associated familial features. None of the patients with sporadic myxoma had unusual freckling or lentiginosis, peripheral myxoid tumours or neurofibromas, or adrenocortical or testicular tumours. The group comprised 51 women and 19 men (ratio, 2·7:1) with a mean age of 56 years.

Discussion

In 1960, Frankenfeld *et al* described a 22 year old white woman with "many dark brown to black freckles on the skin" and synchronous biatrial cardiac myxomas.[11] Although these investigators recognised the rarity of biatrial cardiac tumours, they did not appreciate the significance of the cutaneous hyperpigmentation. In 1973, Rees *et al* reported, in the *British Heart Journal*, the association of cutaneous lentiginosis and a left atrial myxoma in an 18 year old man (fig 1).[27] In 1980, Atherton *et al* described additional features—namely, peripheral tumours and blue naevi—in a 10 year old boy with a synchronous biatrial myxoma (fig 1).[5] In 1982, Schweizer-Cagianut *et al*, unaware of the reports by Rees *et al* and Atherton *et al*, described a single family with cardiac myxomas and familial endocrine neoplasms.[31] In 1984, Rhodes *et al* described another case and raised the question of the possible association of endocrine neoplasms and cardiac myxoma.[28] There had been earlier reports of cardiac myxoma and an association with fibroadenoma of the breast.[29] In 1984, we reported our observations on patients with cardiac myxoma and the belief that a subset of these patients represented a unique subgroup.[3] (In April 1984 this paper was the winner of the Associate Clinical Paper Competition at the meeting of the American College of Physicians in Atlanta.) Other investigators at the Mayo Clinic subsequently reported a review of the features of patients with a complex of myxomas, spotty pigmentation, and endocrine overactivity that included atrial myxoma.[26]

Previous descriptions of syndrome myxoma patients have usually appeared as isolated case reports. To date we have recognised five patients who originally presented at the Mayo Clinic and 39 gleaned from international reports. All 44 had cardiac myxomas; and this report is the first review to concentrate on syndrome myxoma patients with a cardiac myxoma.

A significant feature of this unique subgroup is young age (mean age, 25 *vs* 56 years), and the condition is typically associated with cutaneous lentiginosis, blue naevi, peripheral tumours, and endocrine neoplasms. It is not clear whether these patients have true freckles or lentiginosis; however, we favour the latter interpretation.

Approximately 50% of the patients with syndrome myxoma have multiple cardiac myxomas with a high frequency of biatrial, ventricular, and recurrent myxomas. In our review of published reports we found patient subgroups with cardiac myxoma in which syndrome features were common (syndrome/total): synchronous biatrial myxomas, 13/32 (41%)[38]; ventricular myxomas, 12/77 (16%); age <18 years, 15/66 (23%); recurrent cardiac myxomas, 7/33 (21%)[39]; multiple cardiac myxomas, 17/54 (31%)[39]; and familial cardiac myxomas, 12/30 (40%).[39]

The familial manifestations of the syndrome myxoma patients are particularly interesting. Of 12 reported families with familial cardiac myxoma,[7 9 12 16 25 31 32 40-44] seven (58%) had at least one family member with syndrome myxoma. For this presentation, we excluded relatives of syndrome patients with cardiac myxoma who failed to meet any of the three additional entry criteria (relatives in cases 9, 16, 31, and 32). It is strongly suggested, however, that these relatives are likely to have the syndrome.

This syndrome is probably a "genetic" disorder in the mendelian sense, but much more extensive family studies will be needed before a specific pattern of inheritance can be identified.[45] Individual cases of familial cardiac myxoma[45] may resemble cases of syndrome myxoma: patients with familial cardiac myxoma are younger and have a higher frequency of multiple, biatrial, and ventricular myxomas. For the present, however, the prudent physician should be aware of the possibility of familial occurrence and advise the first degree relatives (parents, siblings, and children) of patients with syndrome myxoma to be examined.

Theories about the pathogenesis of this syndrome remain speculative. Although we believe that syndrome myxoma is a separate entity, many other diseases can have some of the same characteristic features. Other cardiac syndromes with lentiginosis or freckling include electrocardiographic abnormalities,[46] valvar heart disease,[47] hypertrophic cardiomyopathy,[48] and the LEOPARD syndrome[49] (L = lentigenes, E = electrocardiographic conduction defect, O = ocular hypertension, P = pulmonary valve stenosis, A = abnormalities of genitals, R = retardation of growth, and D = deafness). Other entities such as von Recklinghausen's neurofibromatosis,[50] centrofacial lentiginosis,[51] multiple endocrine neoplasia type 3,[52] LEOPARD syndrome,[53] and Peutz-Jeghers[54] syndrome are associated with diffuse lentiginosis and endocrine abnormalities and have an autosomal dominant mode of inheritance. Albright's fibrous dysplasia[55] and neurofibromatosis[56] are associated with hyperpigmented skin lesions, endocrine abnormalities, and soft tissue myxomas. Unlike most of these similar conditions, which are the result of a mutation in the embryonic neural crest,[56 57] myxomas are believed to be of mysenchymal origin. A recent report, however, suggests the possibility of maldevelopment of the neural crest in cardiac myxoma.[58]

We have avoided the use of mnemonic acronyms such as NAME[5] (N = naevi, A = atrial myxoma, M = mucocutaneous myxomas, E = ephelides) or LAMB[28] (L = lentigines, A = atrial myxoma, M = mucocutaneous myxomas, B = blue naevi) to describe the features of syndrome myxoma. Such acronyms describe only some of the manifestations of the syndrome, which appears to be a multisystem condition that may be associated with cardiac myxoma. We therefore believe there is no suitable acronym.

In summary, syndrome myxoma should be suspected in any patient under age 40 years with a cardiac myxoma at a site other than the left atrium. Such patients should be assessed preoperatively for important associations including adrenal integrity, and the surgeon should be made aware of the need for thorough inspection of the heart for multiple subclinical myxomas. Any patient who has familial, recurrent, ventricular, or multiple cardiac myxomas and is unusually freckled or has peripheral noncardiac myxomas or a rare endocrine neoplasm should be followed because syndrome myxoma often recurs. If syndrome myxoma is recognised in an individual, all the first degree relatives should undergo formal evaluation. Cardiac myxoma appears to be only one of the many manifestations of syndrome myxoma.

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References

1 McAllister HA Jr, Fenoglio JJ Jr. Tumours of the cardiovascular system. In: *Atlas of tumour pathology*, Fascicle 15. Washington DC: Armed Forces Institute of Pathology, 1978:1–20.

2 Braunwald E: *Heart disease: a textbook of cardiovascular medicine*. 2nd ed. Philadelphia: WB Saunders, 1984:1457–69.

3 Vidaillet HJ Jr, Seward JB, Fyke E III, Tajik AJ. NAME syndrome (nevi, atrial myxoma, myxoid neurofibroma, ephelides): a new and unrecognized subset of patients with cardiac myxoma. *Minn Med* 1984;**67**:695–6.

4 Abramowitz R, Majdan JF, Plzak LF, Berger BC. Two-dimensional echocardiographic diagnosis of separate myxomas of both the left atrium and left ventricle. *Am J Cardiol* 1984;**53**:379–80.

5 Atherton DJ, Pitcher DW, Wells RS, MacDonald DM. A syndrome of various cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: the NAME syndrome. *Br J Dermatol* 1980;**103**:421–9.

6 Balk AHM, Wagenaar SS, Bruschke AVG. Bilateral cardiac myxomas and peripheral myxomas in a patient with recent myocardial infarction. *Am J Cardiol* 1979;**44**:767–70.

7 Barlow JF, Abu-Gazeleh S, Tam GE, *et al.* Myxoid tumor of the uterus and right atrial myxomas. *SD J Med* July 1983;**36**:9–13.

8 Chandraratna PAN, San Pedro S, Elkins RC, Grantham N. Echocardiographic, angiocardiographic, and surgical correlations in right ventricular myxoma simulating valvar pulmonic stenosis. *Circulation* 1977;**55**:619–22.

9 Crawford FA Jr, Selby JH Jr, Watson D, Joransen J. Unusual aspects of atrial myxoma. *Ann Surg* 1978;**188**:240–4.

10 Dashkoff N, Boersma RB, Nanda NC, Gramiak R, Andersen MN, Subramanian S. Bilateral atrial myxomas: echocardiographic considerations. *Am J Med* 1978;**65**:361–6.

11 Frankenfeld RH, Waters CH, Steiner RC. Bilateral myxomas of the heart. *Ann Intern Med* 1960; **53**:827–38.

12 Grauer K, Grauer MC. Familial atrial myxoma with bilateral recurrence. *Heart Lung* 1983;**12**:600–2.

13 Hanly J, Shaw K, De Buitleir M, Maurer B, Fitzgerald MX. Bi-atrial myxomas presenting as recurrent pulmonary emboli in a girl. *Postgrad Med J* 1984; **60**:147–50.

14 Honey M, Axelrad MA. Intracardiac endodermal heterotopia. *Br Heart J* 1962;**24**:667–70.

15 Jugdutt BI, Rossall RE, Sterns LP. An unusual case of recurrent left atrial myxoma. *Can Med Assoc J* 1975;**112**:1099–100.

16 Laboux L, Mussini-Montpellier J, Michaud JL, Gaillard F, Pelleray C, Cornet E. Myxoma du ventricule droit chez des jumeaux monozygotes: ablation chirurgicale. *Arch Mal Coeur* 1978;**71**:953–9.

17 Levin ME. The development of bilateral adenomatous adrenal hyperplasia in a case of Cushing's syndrome of eighteen years' duration. *Am J Med* 1966; **40**:318–24.

18 Lortscher RH, Toews WH, Nora JJ, Wolfe RR, Spangler RD. Left atrial myxoma presenting as rheumatic fever. *Chest* 1974;**66**:302–3.

19 Lund HZ. Tumors of the skin. In: *Atlas of tumor pathology*, Fascicle 2. Washington DC: Armed Forces Institute of Pathology, 1957:276.

20 Morgan DL, Palazola J, Reed W, Bell HH, Kindred LH, Beauchamp GD. Left heart myxomas. *Am J Cardiol* 1977;**40**:611–4.

21 O'Neill MB Jr, Grehl TM, Hurley EJ. Cardiac myxo-

mas: a clinical diagnostic challenge. *Am J Surg* 1979;**138**:68–74.

22 Pavie A, Escande G, Cham B, *et al.* Les myxomes de l'oreillette droite: à propos de 3 observations; revue de la littérature. *Arch Mal Coeur* 1981;74:265–72.

23 Peterson LL, Serrill WS. Lentiginosis associated with a left atrial myxoma. *J Am Acad Dermatol* 1984;**10**:337–40.

24 Ports TA, Schiller NB, Strunk BL. Echocardiography of right ventricular tumours. *Circulation* 1977; **56**:439–47.

25 Proppe KH, Scully RE. Large-cell calcifying Sertoli cell tumor of the testis. *Am J Clin Pathol* 1980;74:607–19.

26 Carney JA, Gordon H, Carpenter PC, Shenoy BV, Go VLW. The complex of myxomas, spotty pigmentation, and endocrine overactivity. *Medicine (Baltimore)* 1985;**64**:270–83.

27 Rees JR, Ross FGM, Keen G. Lentiginosis and left atrial myxoma. *Br Heart J* 1973;**35**:874–6.

28 Rhodes AR, Silverman RA, Harrist TJ, Perez-Atayde AR. Mucocutaneous lentigines, cardiomucocutaneous myxomas, and multiple blue nevi: the "LAMB" syndrome. *J Am Acad Dermatol* 1984; **10**:72–82.

29 Roper CL, Camp FA, Kempson RL. Atrial myxoma associated with fibroadenomas of the breast. *Mo Med* 1965;**62**:113–6.

30 Bahl OP, Oliver GC, Ferguson TB, Schad N, Parker BM. Recurrent left atrial myxoma: report of a case. *Circulation* 1969;**40**:673–6.

31 Schweizer-Cagianut M, Salomon F, Hedinger CE. Primary adrenocortical nodular dysplasia with Cushing's syndrome and cardiac myxomas: a peculiar familial disease. *Virchows Arch [A]* 1982;**397**:183–92

32 Tway KP, Shah AA, Rahimtoola SH. Multiple biatrial myxomas demonstrated by two-dimensional echocardiography. *Am J Med* 1981;71:896–9.

33 Zager J, Smith JO, Goldstein S, Franch RH. Tricuspid and pulmonary valve obstruction relieved by removal of a myxoma of the right ventricle. *Am J Cardiol* 1973;**32**:101–4.

34 Zajtchuk R, Fitterer JD, Strevey TE, Nelson WP. Bilateral atrial myxomas: preoperative diagnosis and successful removal. *J Thorac Cardiovasc Surg* 1975;**69**:291–4.

35 Miller JI, Mankin HT, Broadbent JC, Giuliani ER, Danielson GK. Primary cardiac tumors: surgical considerations and results of operation. *Circulation* 1972;**45** (suppl 1):134–8.

36 St John Sutton MG, Mercier L-A, Giuliani ER, Lie JT. Atrial myxomas: a review of clinical experience in 40 patients. *Mayo Clin Proc* 1980;55:371–6.

37 Fyke FE III, Seward JB, Edwards WD, *et al.* Primary cardiac tumours: experience with 30 consecutive patients since the introduction of two-dimensional echocardiography. *J Am Coll Cardiol* 1985; 5:1465–73.

38 Vidaillet HJ Jr, Seward JB, Fyke FE III, Tajik AJ. Bilateral myxomas: much more than cardiac myxomas in either side of the atrial septum: a "syndrome" myxoma? [Abstract]. *Chest* 1985;**88**:10S.

39 McCarthy PM, Piehler JM, Schaff HV, *et al.* The significance of multiple, recurrent, and "complex" cardiac myxomas. *J Thorac Cardiovasc Surg* 1986;**91**:389–6.

40 Kleid JJ, Klugman J, Haas J, Battock D. Familial atrial myxoma. *Am J Cardiol* 1973;**32**:361–4.

41 Liebler GA, Magovern GJ, Park SB, Cushing WJ, Begg FR, Joyner CR. Familial myxomas in four siblings. *J Thorac Cardiovasc Surg* 1976;71:605–8.

42 Powers JC, Falkoff M, Heinle RA, *et al.* Familial cardiac myxoma: emphasis on unusual clinical manifestations. *J Thorac Cardiovasc Surg* 1979;77:782–8.

43 Siltanen P, Tuuteri L, Norio R, Tala P, Ahrenberg P, Halonen PI. Atrial myxoma in a family. *Am J Cardiol* 1976;**38**:252–6.

44 Farah MG. Familial atrial myxoma. *Ann Intern Med* 1975;**83**:358–60.

45 Carney JA. Differences between nonfamilial and familial cardiac myxoma. *Am J Surg Pathol* 1985;9:53–5.

46 Walther RJ, Polansky BJ, Grots IA. Electrocardiographic abnormalities in a family with generalized lentigo. *N Engl J Med* 1966;**275**:1220–5.

47 Forney WR, Robinson SJ, Pascoe DJ. Congenital heart disease, deafness, and skeletal malformations: a new syndrome? *J Pediatr* 1966;**68**:14–26.

48 St John Sutton MG, Tajik AJ, Giuliani ER, Gordon H, Su WPD. Hypertrophic obstructive cardiomyopathy and lentiginosis: a little known neural ectodermal syndrome. *Am J Cardiol* 1981;**47**:214–7.

49 Gorlin RJ, Anderson RC, Blaw M. Multiple lentigenes syndrome. *Am J Dis Child* 1969;**117**:652–62.

50 Fienman NL, Yakovac WC. Neurofibromatosis in childhood. *J Pediatr* 1970;**76**:339–46.

51 Dociu I, Galaction-Nitelea O, Şirjiţă N, Murgu V. Centrofacial lentiginosis: a survey of 40 cases. *Br J Dermatol* 1976;**94**:39–43.

52 Khairi MRA, Dexter RN, Burzynski NJ, Johnston CC Jr. Mucosal neuroma, pheochromocytoma and medullary thyroid carcinoma: multiple endocrine neoplasia type 3. *Medicine (Baltimore)* 1975; **54**:89–112.

53 Voron DA, Hatfield HH, Kalkhoff RK. Multiple lentigines syndrome: case report and review of the literature. *Am J Med* 1976;**60**:447–56.

54 Scully RE. Sex cord tumor with annular tubules: a distinctive ovarian tumor of the Peutz-Jeghers syndrome. *Cancer* 1970;**25**:1107–21.

55 Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females: report of five cases. *N Engl J Med* 1937;**216**:727–46.

56 Kissel P, Andre JM, Jacquier A. *The neurocristopathies.* New York: Masson Publishing, 1981.

57 Bolande RP. The neurocristopathies: a unifying concept of disease arising in neural crest maldevelopment. *Hum Pathol* 1974;5:409–29.

58 Harrison LH Jr, Said SI, Ezekowitz MD, Krous HF. Vasoactive intestinal polypeptide in cardiac myxoma. *J Thorac Cardiovasc Surg* 1985;**89**:800–6.

Br Heart J 1987;57:256–63

Sarcoidosis: a pattern of clinical and morphological presentation

HANNAH VALANTINE, WILLIAM J McKENNA, PETROS NIHOYANNOPOULOS, ANDREW MITCHELL,* RODNEY A FOALE, M J DAVIES, CELIA M OAKLEY

From the Division of Cardiovascular Disease, Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY The diagnosis of cardiac sarcoidosis, particularly when there is no overt systemic involvement, is frequently delayed because of its varied manifestations. Focal left ventricular wall motion abnormalities were recognised in five patients with sarcoidosis. Three patients showed abnormal regional wall motion in the basal portion of the ventricular septum and free wall with sparing of the apex. The angiographic appearances supported the echocardiographic findings which were atypical of ischaemic heart disease. The remaining two patients both had diffuse left ventricular hypokinesia, with a focal abnormality that was most pronounced in the anteroapical region; this pattern is often seen with coronary disease.

The recognition by echocardiography or angiography of focal abnormalities of wall motion affecting the basal portion of the ventricular septum should suggest the possibility of myocardial sarcoidosis even in the absence of recognised systemic manifestations.

Focal abnormalities of left ventricular wall motion are uncommon except in coronary artery disease in which the distribution is dependent on coronary artery anatomy. It is therefore unusual to find wall motion abnormalities localised to the basal part of the septum with sparing of the apical portion. This report of five cases shows that although sarcoid granuloma can occur anywhere in the heart a pattern of fibrosis distinct from coronary disease may be recognised by echocardiography and angiography.

Patients and methods

We studied five men aged 29, 36, 37, 45, and 46 years. One was black and the remainder were white. Systemic sarcoidosis had been diagnosed because at least two organ systems were affected and there was either positive lymph node histology or a Kveim test. All patients underwent cardiac catheterisation, coronary angiography, and cross sectional echocardiography. Three patients shared several clinical characteristics. None of these three had clinical evidence of heart failure. All had normal physical examination, normal laboratory indices of bone marrow, renal, and hepatic function. All had left anterior hemiblock and right bundle branch block. Left ventricular end diastolic and pulmonary artery pressures were normal and there was no disease of the major epicardial coronary arteries. The table summarises the investigations that were performed to assess disease activity and distribution.

In patient 1 systemic sarcoidosis was not diagnosed during life. He presented with a two year history of palpitation and ventricular tachycardia associated with syncope and evidence of a progressive conduction system disturbance. During cross sectional echocardiography from the parasternal long axis view (fig 1a) the basal part of the ventricular septum was thin and akinetic with increased echo reflectivity and paradoxical systolic motion. The same abnormality was seen in serial short axis views at the level of mitral valve and papillary muscle (fig 2). The apical third of the ventricular septum, the posterior wall of the ventricle, and the right ventricular free wall were normal. Left

Requests for reprints to Dr William J McKenna, Division of Cardiovascular Disease, Royal Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London W12 0HS

*Present address: Department of Cardiology, Harefield Hospital, Harefield, Uxbridge, Middlesex

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Table *Investigations to assess activity and extent of sarcoidosis*

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*
ESR	4	10	8	70	10
SACE	ND	33	88	58	ND
Gallium uptake	ND	Normal	Matched uptake in left lung hilum, and paratracheal area	ND	ND
Thallium uptake*	Septum and free wall	ND	Septum	Anteroapical and free wall	ND
Chest *x* ray	Recurrent pulmonary infiltrates	Normal	Hilar lymphadenopathy, pulmonary infiltrates	Hilar lymphadenopathy	Hilar lymphadenopathy
Cardiothoracic ratio	19/30	15/30	14/28	20/30	18/30
Pulmonary function tests	ND	Normal†	Decreased lung volumes and gas transfer	Decreased lung volumes and gas transfer	Normal

*Thallium scans showed decreased uptake during exercise without recovery in the designated areas.
†At diagnosis chest *x* ray showed right hilar lymphadenopathy and a right apical infiltrate.
SACE, serum angiotensin I converting enzyme (normal range = 16–53 units/ml); ND, not done; ESR, erythrocyte sedimentation rate.

ventricular angiography in the right anterior oblique projection (fig 3a) showed poor contraction of the anterobasal and posterobasal segments whereas the apical segments contracted normally. Coronary angiography was normal. Endocardial resection for resistant ventricular tachycardia was complicated by a low output state and the patient died during operation.

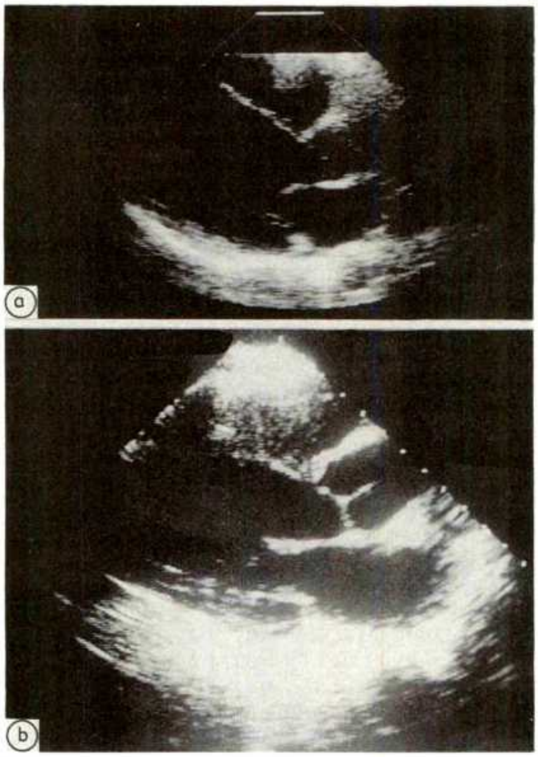

Fig 1 *Echocardiographic appearances in the parasternal long axis views in patients 1(a) and 3(b) showing thinning of the basal portion of the ventricular septum, which was pronounced in patient 1.*

At necropsy the heart weighed 583 g. The basal ventricular septum was thick and replaced by fibrous tissue (fig 4) that extended into the basal part of the posterior wall. This mirrored the echocardiographic and angiographic appearances. Histological examination confirmed replacement of this part of the septum by dense fibrous tissue. The remainder of the myocardium showed focal scarring with an occasional giant cell but no granulomas. Typical sarcoid granulomas were, however, present in the lungs, spleen, mediastinal lymph nodes, and liver.

In patient 2 sarcoidosis of the heart had been diagnosed 10 years earlier when he presented with supraventricular and ventricular arrhythmia, progressive conduction disturbance, and pulmonary sarcoidosis (table). He was referred for control of ventricular arrhythmias that had failed to improve on increasing doses of steroids. Cross sectional echocardiography in the parasternal long axis view (fig 5) showed that the basal portion of the ventricular septum was thin, akinetic, and aneurysmal, and clearly protruded into the right ventricle in systole, while the apical part was of normal thickness and contracted normally. This focal ventricular abnormality was also seen in short axis views at the level of mitral valve and papillary muscle (fig 6). The cardiac apex was seen to be contracting normally. Angiographic examination showed that the basal part of the left ventricle was dilated and aneurysmal and the apical portion contracted normally (fig 3b). He was treated with mexiletine and amiodarone. Ventricular arrhythmia was inadequately controlled and he died suddenly. At necropsy the heart weighed 500 g. The basal two thirds of the ventricular septum was thin and extensively replaced by fibrous tissue that extended into the basal part of the posterior wall. Elsewhere the myocardium appeared to be normal and no granulomas were found in histological sections of the heart. Examination of the lungs, mediastinum, liver, and spleen showed extensive replacement of the normal tissue by the typical non-caseating granuloma of sarcoidosis.

Patient 3 was known to have had pulmonary sarcoidosis for 14 years before his presentation with syncope, complete heart block, and a soft systolic murmur at the apex. Echocardiography from the parasternal long axis view (fig 1b) showed that the ventricular septal dimension was within normal limits, but in its basal portion the septum was akinetic and showed increased echo reflectivity. The apical third of the ventricular septum, posterior wall, and right ventricular free wall were normal. The short axis views (fig 7) at the level of the mitral valve also showed the same akinetic and echo-dense ventricular septum which was of normal dimensions at the level of the mitral valve, but at the papillary muscle level the septum was thin and akinetic. Appearances were normal at the level of the apex. Left ventricular angiography showed mild impairment of contraction of the basal portion of the left ventricle with mild mitral regurgitation (fig 3c). A biopsy specimen of the right ventricle contained epitheloid giant cells and fibrous granulomas characteristic of sarcoidosis. The patient has been symptom free after the insertion of a permanent pacemaker.

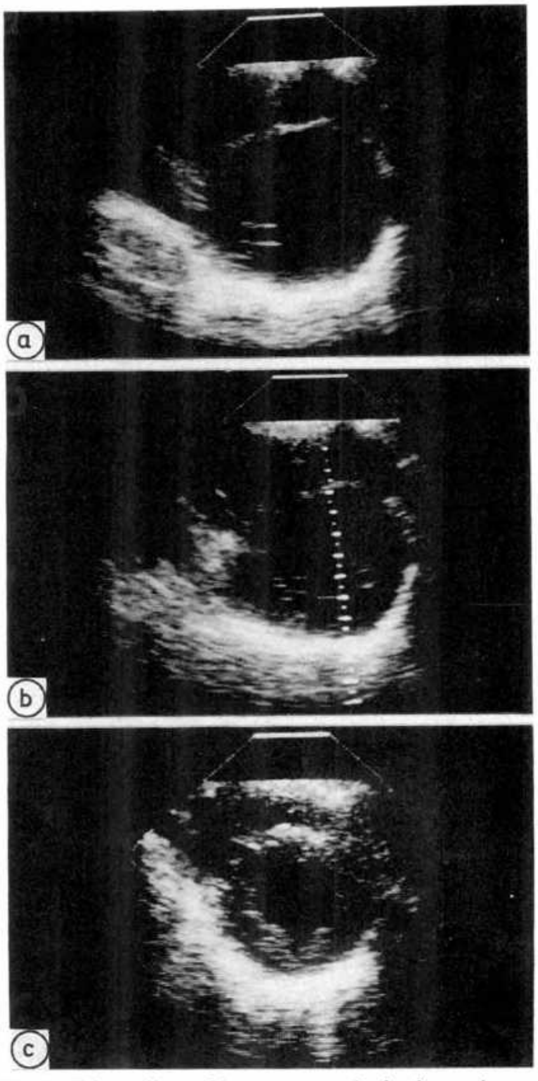

Fig 2 *Echocardiographic appearances in the short axis views in patient 1 at the level of mitral valve (a), papillary muscle (b), and apex (c). There was no systolic thickening of the septum at the mitral and papillary muscle level. In contrast apical contraction was normal.*

The clinical features and mode of presentation were different in the remaining two patients. Patient 4 presented with an acute systemic illness characterised by fever, high erythrocyte sedimentation rate (70 ml/h), hilar lymphadenopathy, and congestive cardiac failure. There were Q waves on the electrocardiogram that simulated anterior myocardial infarction. Echocardiography showed septal hypertrophy and mild global hypokinesia and there was a fixed thallium perfusion defect of the anteroapical region of the left ventricle. Angiographic examination of the left ventricle showed a considerable increase in end systolic volume with extensive anteroapical akinesia, and hypokinesia of the remainder of the ventricle. The result of coronary arteriography was normal. A biopsy specimen of the myocardium showed diffuse interstitial fibrosis but no granulomas, and the diagnosis of sarcoidosis was based on a biopsy specimen of the mediastinal lymph nodes.

Patient 5 presented with ventricular tachycardia and no evidence of congestive cardiac failure. An electrocardiogram showed T wave inversion in the inferior and lateral leads and voltage criteria that were characteristic of hypertrophy of the left ventricle but no conduction abnormality. Cross sectional echocardiography showed global hypokinesia, which was confirmed by angiography, with akinesia and calcification of the apex. The haemodynamic function of the right and left heart and the results of coronary arteriography were normal. A biopsy specimen of the myocardium showed diffuse interstitial fibrosis only. Systemic sarcoidosis was diagnosed on the basis of bilateral hilar lymphadenopathy and a positive Kviem test.

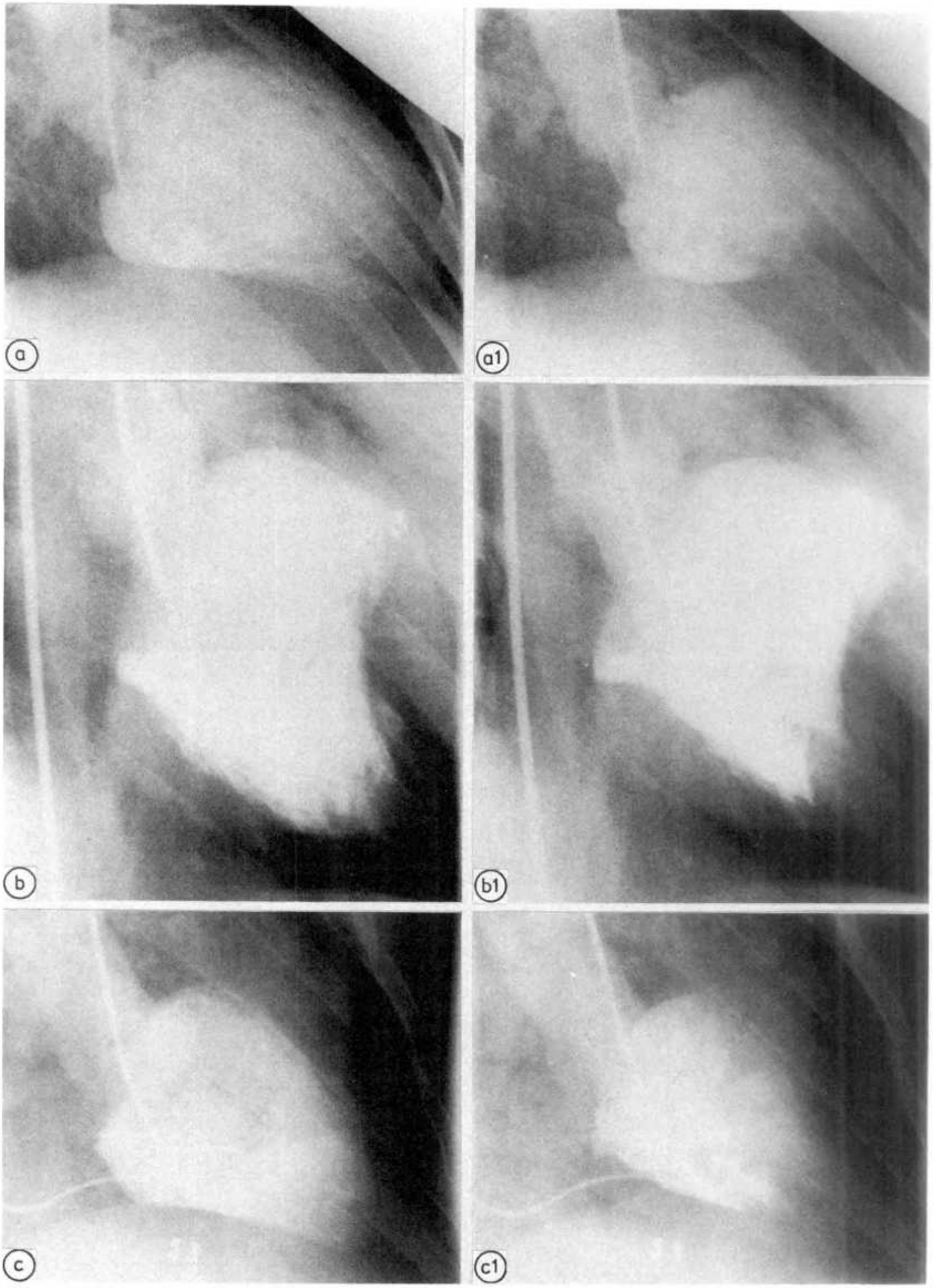

Fig 3 *Left ventricular angiograms of patients 1, 2, and 3 (a, b, and c respectively) in systole (right) and diastole (left) in the right anterior oblique projection, showing impaired contraction of the base of the heart, which is most pronounced in patient 2.*

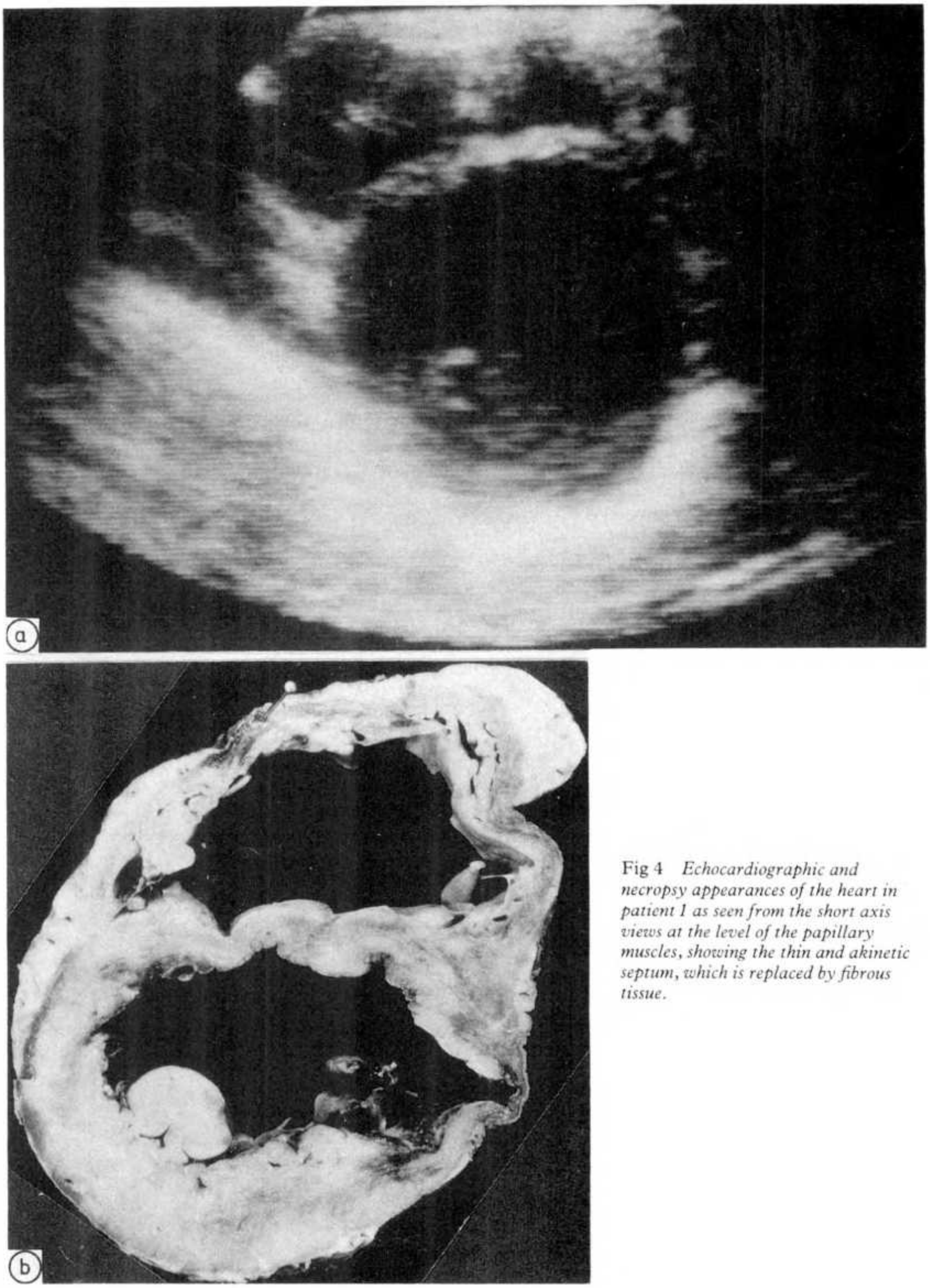

Fig 4 *Echocardiographic and necropsy appearances of the heart in patient 1 as seen from the short axis views at the level of the papillary muscles, showing the thin and akinetic septum, which is replaced by fibrous tissue.*

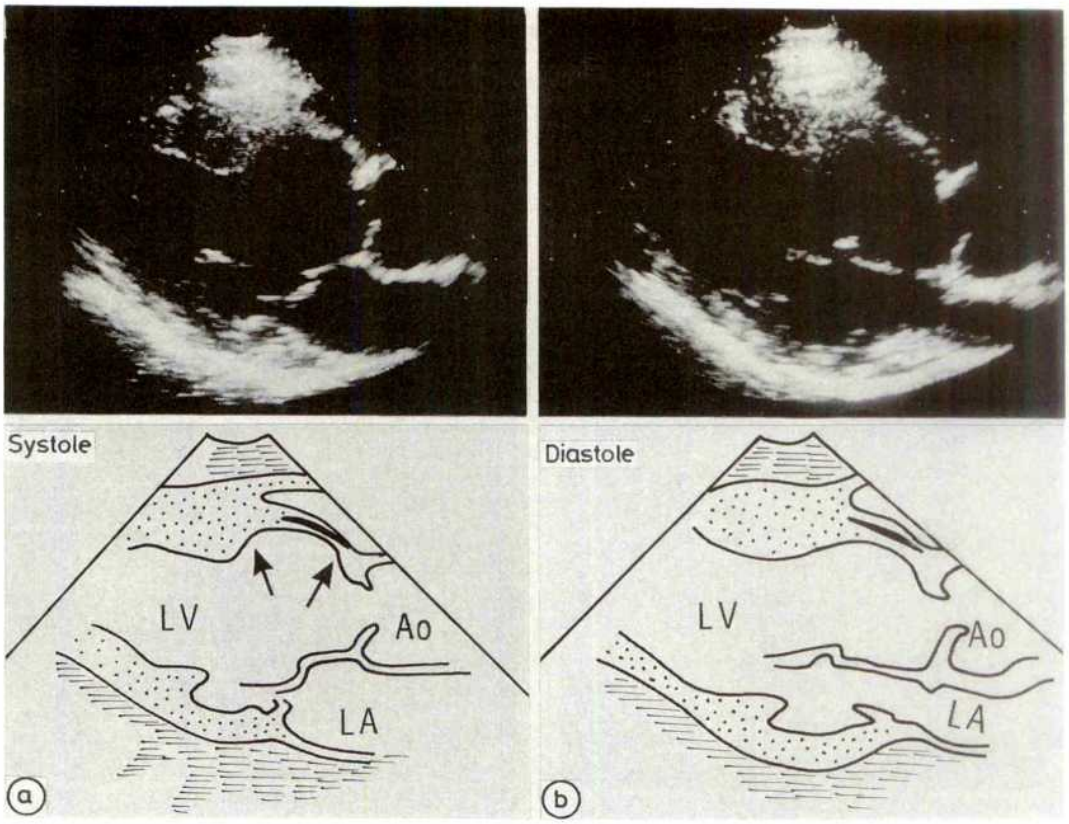

Fig 5 *Long axis views of systolic and diastolic frames in patient 2.*

Discussion

Sarcoidosis is a multisystem granulomatous disorder of unknown cause. The frequency of clinical cardiac involvement in patients with systemic sarcoidosis is low (1·5%).[1 2] Most (80%) patients with cardiac sarcoidosis have conduction disturbance or arrhythmia[3-8] and/or impaired cardiac function (31%).[5-9] Patients have also presented with mitral stenosis caused by leaflet granuloma[10] or with mitral regurgitation caused by infiltration of the papillary muscle.[11] In patients with cardiac sarcoid the risk of sudden death is considerable.[3] An additional 23% of patients with systemic sarcoidosis will have isolated sarcoid granulomas that are detectable only by histological examination of the heart[1] but the proportion of positive cases probably varies with the extent to which the myocardium is sampled at necropsy.

The wide range of clinical manifestations of cardiac sarcoidosis evident from this report of five cases is consistent with the varied distribution and morphological features of the abnormalities. In patients who die in the active phase of myocardial sarcoidosis granulomas may either be distributed evenly throughout the myocardium or occur as a localised mass, commonly in the basal portion of the ventricular septum.[3 5 12] The frequency of sudden death reflects the high risk that the conduction system will be affected in both the focal and diffuse forms.[3]

This acute phase of myocardial sarcoidosis will resolve either as diffuse interstitial fibrosis of the myocardium and a generalised hypokinesia of the ventricle or as a localised fibrous scar with focal contraction abnormalities. Diffuse fibrosis is difficult to distinguish from dilated cardiomyopathy. Focal lesions may also be difficult to distinguish in life from ischaemic heart disease but the lesion in the basal portion of the septum in cases 1–3 is in an unusual site for old infarction and is typical of sarcoidosis. For these reasons and because of the presence of normal coronary arteriograms the scars in patients

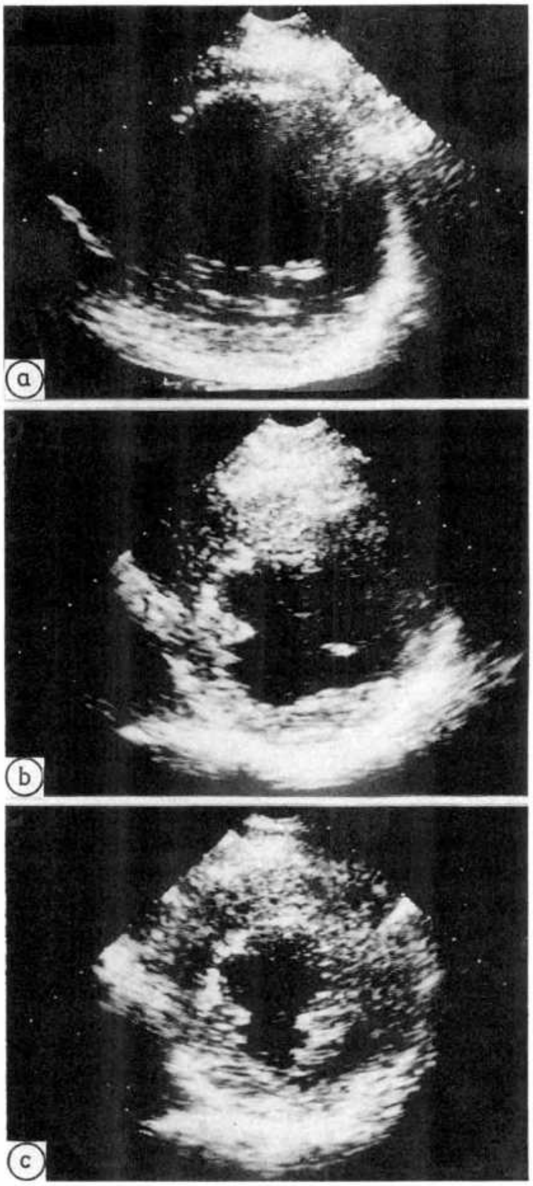

Fig 6 *Short axis views in patient 2. Legend as for fig 2.*

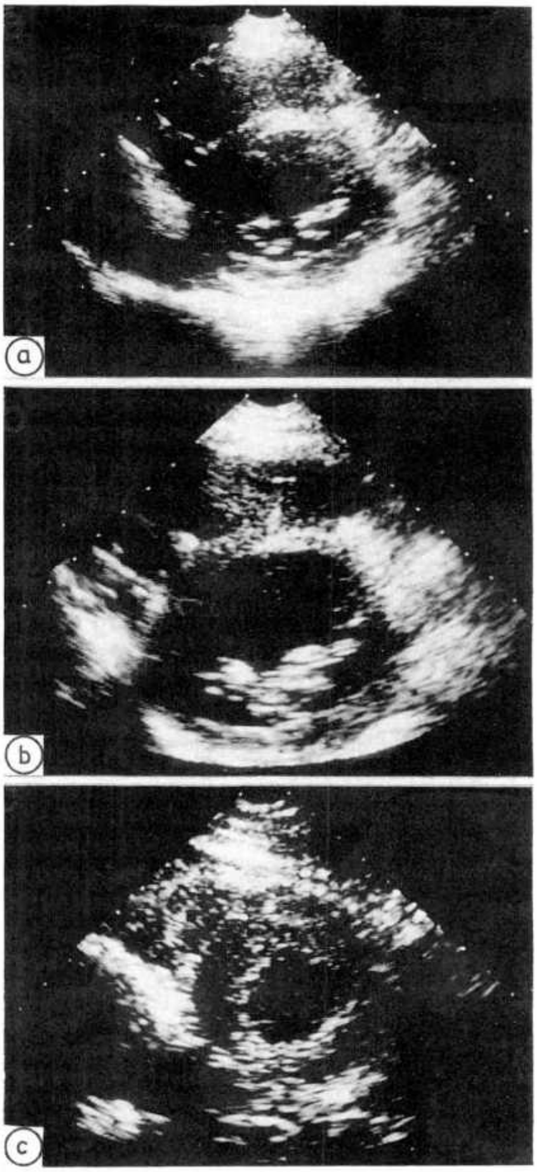

Fig 7 *Short axis views in patient 3. Legend as for fig 2.*

1–3 were taken to indicate healed sarcoidosis though no active granulomas were found in the myocardium.

The acute and more chronic forms of myocardial sarcoid have been linked to four histological patterns.[13] An exudative type (lymphocytic infiltration with oedema) and a granulomatous type (granulomata with epithelial cells) are associated with systemic disease and characterised by a subacute course with clear clinical evidence of multi-organ involvement. The chronic fibrous types (with and without giant cells) are associated with the chronic insidious course seen in cases 1–3. The papillary muscles and right ventricle are also commonly found to contain granulomas at necropsy. Case 3 had clinical and echocardiographic evidence of papillary muscle dysfunction as well as right ventricular involvement and typical granulomas were found in biopsy specimens of the right ventricle.

The use of steroids in cardiac sarcoid has not been systematically evaluated. Retrospective analysis, however, suggests that steroids promote healing of granulomas but the concomitant development of fibrous tissue may be complicated by aneurysm formation[5]; this is an otherwise rare complication. Patients 2 and 3 received long term corticosteroid treatment. Both showed thinning of myocardial segments. In patient 2 there was an intracardiac aneurysm of the basal septum that bulged into the outflow tract of the right ventricle; at necropsy this segment was found to be replaced with fibrous tissue. Though granulomas were detected in other organs they were not found in the heart. Patient 1 also had myocardial thinning caused by fibrous tissue replacement and multiple organ granulomas but no cardiac ones. He had not been given steroids, however. These findings are consistent with published reports which suggest that steroids promote healing, which may be complicated by the development of an aneurysm. They also indicate that steroids are not a prerequisite for such a course and they raise the question of the usefulness of steroids once myocardial thinning and aneurysm have developed.

Patient 2 had refractory ventricular arrhythmia and died suddenly. Patients are usually only referred for transplantation when poor and deteriorating left ventricular function and the ensuing shortness of breath, fatigue, and oedema indicate that they will die soon. Referral for transplantation is much more difficult and therefore less often acted upon when life threatening arrhythmia cannot be controlled. The argument for transplantation is more cogent if the arrhythmia is caused by a process which itself may be advancing, such as cardiac sarcoidosis. We considered transplantation in patient 2 but did not act upon it immediately. His death was sudden but predictable. Hearts have been successfully transplanted into patients with cardiac sarcoidosis[14] but we delayed too long.

Our index patient, patient 1, had conduction disturbance and ventricular tachycardia in the absence of recognised systemic sarcoidosis. The diagnosis of cardiac sarcoid is seldom missed when this constellation of changes coexists with systemic sarcoidosis. In the absence of systemic sarcoid these cardiac abnormalities are not specific and are more likely to have other causes. The focal abnormality of wall motion localised to the basal portion of the ventricular septum that we described is unusual in coronary artery disease and should suggest the diagnosis of cardiac sarcoid even when there are no systemic changes.

We are grateful to Professor John F Goodwin for permission to publish details of case 1.

References

1 Silverman KJ, Hutchins GM, Buckley BH. Cardiac sarcoid: a clinicopathological study of 84 unselected patients with systemic sarcoidosis. *Circulation* 1978,58:1204–11.

2 Fleming HA. Sarcoid heart disease. *Br Heart J* 1974;36:54–68.

3 Lie JT, Hunt D, Valantine PA. Sudden death from cardiac sarcoidosis with involvement of the conduction system. *Am J Med Sci* 1974;267:123–8.

4 Lull RJ, Dunn BE, Gregoratus G, Cox WA, Fisher GW. Ventricular aneurysm due to cardiac sarcoidosis with surgical cure of refractory ventricular tachycardia. *Am J Cardiol* 1972;30:282–7

5 Roberts WC, McAllister HA, Ferrans VJ Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group I) and review of 78 previously described necropsy patients (group II). *Am J Med* 1977;63:86–108.

6 James TN. De Subitaneis Mortibus. XXV. Sarcoid heart disease. *Circulation* 1977;56:320–6.

7 McTaggart DR. Sarcoidosis with cardiac involvement. *Med J Aust* 1973;ii:689–90.

8 Miller A, Jackler I, Chuang M. Onset of sarcoidosis with left ventricular failure and multisystem involvement. *Chest* 1976;70:302–4.

9 Ahmed SS, Rozefort R, Taclob LT, Brancato RW. Development of ventricular aneurysm in cardiac sarcoidosis. *Angiology* 1977;28:323–9.

10 Fitchett DH, Oakley CM. Granulomatous mitral valve obstruction. *Br Heart J* 1976;38:112–6.

11 Raftery EB, Oakley CM, Goodwin JF. Acute subvalvar mitral incompetence. *Lancet* 1966;ii:360–5.

12 Ghosh P, Fleming HA, Gresham GA, Stovin PGI. Myocardial sarcoidosis. *Br Heart J* 1972;34:769–73.

13 Matsui Y, Iwai K, Tachibana T, *et al.* Clinicopathological study of fatal myocardial sarcoidosis. *Ann NY Acad Sci* 1976;278:455–69.

14 Gokel JM, Reichart B, Struck E. Human cardiac transplantation—evaluation of morphological changes in serial endomyocardial biopsies. *Pathol Res Pract* 1985;17:354–64.

Br Heart J 1987;57:264–9

Quantitative structural analysis of collagen in chordae tendineae and its relation to floppy mitral valves and proteoglycan infiltration

PETER WHITTAKER,* DEREK R BOUGHNER,†* D GARTH PERKINS,‡
PETER B CANHAM*

*From the Departments of *Biophysics, †Medicine, and ‡Pathology, University of Western Ontario, London, Ontario, Canada*

SUMMARY Imbibition analysis, a polarised light microscopy technique, was used to examine the molecular organisation of collagen in normal and diseased mitral valve chordae tendineae. A single strut chorda from each of 23 valves (14 from necropsy specimens and nine from valve replacement surgery) was studied. The degree of molecular organisation of collagen in unstained 7 μm sections of the chordae was assessed by measuring the retardation of polarised light by the sample. Sections from each tendon were examined, after staining with Movat's pentachrome, for the presence of proteoglycan infiltration and classified as normal or abnormal on that basis. The imbibition analysis results were grouped accordingly. The retardation in the collagen in the seven chordae with proteoglycan infiltration was significantly lower than in the 16 normal chordae, indicating decreased molecular organisation. Five of the seven abnormal chordae with proteoglycan infiltration and decreased retardation were from patients with floppy mitral valves; the other two were from normal necropsy specimens.

Although proteoglycan infiltration may not be a specific marker for floppy valve disease, its presence is associated with decreased molecular organisation of collagen in the chordae. Degradation of the ground substance bound to the collagen is the most plausible explanation for the measured optical changes.

The widespread occurrence of floppy mitral valves has provoked much interest, both in its clinical aspects and in the pathological process(es) that cause it. No single defect, however, has been identified as the main factor causing floppy valves. Since Read *et al* first observed mitral prolapse and introduced the term floppy valve,[1] there have been many suggestions regarding the nature of the abnormality. One histological feature that is frequently associated with floppy valves is the presence of large aggregated amounts of proteoglycans (often called myxomatous infiltration). The accumulation of proteoglycans was first thought to be the primary lesion in floppy valves. However, myxomatous change is not seen in every floppy valve and may also be found in valves without clinical manifestation of the condition.[2] Based on their morphological and histological study of mitral valves, King *et al* proposed that collagen dissolution in the valves and chordae tendineae was the basic pathological process.[2] They did not, however, identify the exact nature of the collagen dissolution. Genetic collagen abnormalities such as Marfan syndrome[3] and the various types of Ehlers-Danlos syndrome[4] have also been associated with floppy valves, but the nature of this relation remains unclear. Hammer *et al* suggested that the collagen in the valve apparatus was abnormal because of an absence of type III and type V collagen,[5] but this conclusion was based on the study of a single mitral valve with ruptured chordae. A later study by Lee *et al*, with a larger sample size, showed no difference in the collagen type composition of normal and

Requests for reprints to Dr Peter Whittaker, Wayne State University Medical School, Myocardial Ischemia Research Laboratory, Cardiology Division, Harper Hospital, 3990 John R, Detroit, MI 48201, USA.

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floppy valves.[6] Henney *et al* found that there was an increased synthesis of collagen in the valve complex.[7] Others, however, have reported evidence for a breakdown in the normal collagenous structure of the chordae.[8 9] These groups used electron microscopy to demonstrate extensive degradation of the collagen in ruptured chordae, which they suggested could be due to enzyme activity. Guthrie and Edwards proposed that chordal elongation observed in mitral valve prolapse was the result of abnormal chordal tension caused by the prolapsing leaflet.[10] This seems unlikely unless the collagen in the chordae was also abnormal, since mechanical testing has shown that normal chordae are relatively stiff at strain values above 15%.[11]

The one factor common to these proposals is that collagen structure is a key element in floppy valves. Since the above studies did not reveal a consistent abnormality of collagen fibre structure the problem could be at the molecular level. We used imbibition analysis, a polarised light microscopy technique, to examine the molecular organisation of collagen in the chordae tendineae of normal and floppy mitral valves. This method exploits the anisotropic molecular organisation of collagen, which makes it birefringent and hence visible in the polarising microscope. Changes in molecular organisation that would not be seen with ordinary light microscopy can be observed and quantified by the use of polarised light.

Patients and methods

A single randomly selected strut chorda was removed from each of 23 mitral valves. Of these specimens, 14 (eight from men and six from women) were obtained at necropsy from patients who had died from non-cardiac causes (age range 26–92), and nine (five men, four women) came from patients undergoing valve replacement for mitral valve disease (age range 58–81). In the latter group, the clinical diagnosis was floppy valve disease in six patients and rheumatic mitral valve disease in the remaining three.

Each of the selected chordae tendineae was fixed in 10% neutral buffered formalin. The chordae were processed for paraffin embedding and then sectioned longitudinally at a thickness of 7 μm. Longitudinal sectioning resulted in the collagen fibres lying in the plane of the section. The sections were mounted on strain free glass slides. Immediately before mounting the slides were smeared with albumin fixative, which helped the section adhere to the slide during the measuring procedures. Sections from each of the chordae were then examined by the following techniques.

IMBIBITION ANALYSIS

Theory

When linearly polarised light enters a material such as collagen, which has an anisotropic molecular organisation, the light is resolved into two rays (called the ordinary and extraordinary rays) that are polarised in mutually perpendicular planes.[12] This property of birefringent materials forms the basis of the method of examining molecular organisation. The two rays travel at unequal velocities, because of the anisotropy of the tissue, and a phase difference is therefore introduced between them. The difference in the two velocities depends on the molecular organisation of the material. Hence, by measuring the retardation produced, which is proportional to the phase difference, the molecular organisation of different samples may be compared. The retardation, Γ, is given by the formula, $\Gamma = t\,(n_e - n_o)_i$ (equation 1),[12] where t is the section thickness and n_e and n_o are the refractive indices of the two rays. The term $(n_e - n_o)_i$ is called the intrinsic birefringence and is a characteristic property of the tissue. The measured retardation may be altered by staining and is also dependent on orientation. Therefore, to ensure that the retardation was solely due to the intrinsic molecular organisation of the collagen itself, we studied unstained sections. To eliminate orientation effects the chordae were sectioned longitudinally so that the collagen fibres lay in the section plane.

Form birefringence also contributes to retardation. Form birefringence arises from the difference in refractive index between the material being studied and the surrounding medium. The contribution of form birefringence $(n_e - n_o)_f$ to the retardation is given by $(n_1^2 - n_2^2)^2F$ (equation 2), where n_1 is the refractive index of the material, n_2 the refractive index of the mounting medium, and F is a form factor,[13] which depends on volume fractions of the different components and the shape of the fibres. The mathematics developed to calculate F assume that a two component system is being studied—that is the surrounding or imbibing medium and the material. Because of its bound ground substance collagen is a more complex system and the equations cannot be rigorously applied. However, when $n_1 = n_2$ the form birefringence will be zero regardless of the value of F, and so only the intrinsic birefringence will contribute to the retardation. Therefore, if retardation in collagen is measured in a series of different media with different refractive indices the retardation at the minimum value on the graph in which retardation is plotted against refractive index will be proportional to the intrinsic birefringence, and hence will be related to the molecular organisation. This procedure is called

Table *The media used in the imbibition analysis and their refractive indices*

Imbibing medium	*Refractive index*
Water	1·33
20% glycerol	1·36
40% glycerol	1·39
60% glycerol	1·42
80% glycerol	1·44
100% glycerol	1·46
Paraffin oil	1·48

imbibition analysis and graphs of retardation versus refractive index are called form birefringence curves.

Measuring procedure

Retardations were measured by the method of de Sénarmont.[12] A Nikon Optiphot-pol microscope with a 40× objective, a quarter wave plate, and a monochromatic light source (λ = 546 nm) were used. The sections were first cleared of embedding wax with xylene, then washed and soaked in water until the tissue was fully imbibed—that is further soaking produced no change in retardation. The time required to achieve this state was one hour.[14] The slide was then removed from the water and a coverslip was placed over the section to prevent it from drying. For each section, the retardation of the collagen was measured at ten different locations in the tendon and an average was calculated. The coverslip was then removed, the section was imbibed in another fluid with a higher refractive index, and the retardation measured as before. This process was repeated through a series of imbibing media with successively higher refractive indices. The media used are listed in the table with their refractive indices (measured by an Abbe refractometer). We were guided to our choice of imbibing fluids by the work of Vidal.[15] Form birefringence curves were drawn for each of the samples. The results from the imbibition analysis were compared by means of t tests.

Picrosirius red staining

Sections from each of the 23 chordae were stained with picrosirius red,[16] which is specific for collagen when used with polarised light.[17] In 7 μm sections, normal type I collagen fibres appear orange or red, while thinner degraded collagen fibres will appear yellow or green.[18] This stain has previously been used to demonstrate collagen degradation by bacterial collagenase in sections of cirrhotic liver[19] and by leucocytes in the cervix during parturition.[20] The sections of chordae tendineae were examined for the presence of yellow or green fibres.

Pathological classification

Sections of the 23 chordae were stained with haematoxylin and eosin and with Movat's pentachrome stain, which contains alcian blue (pH 2·9)—a stain used to demonstrate the presence of proteoglycans. Each of the haematoxylin and eosin and Movat's pentachrome stained sections were examined without knowledge of their source by one of us (DGP) for evidence of proteoglycan infiltration. Each of the chordae was then classified as being normal or abnormal on the basis of the presence of proteoglycan infiltration.

Results

The results from the imbibition analysis were divided into "normal" and "abnormal" groups according to the histological classification. The average form birefringence curve for each group was then calculated (fig 1). The retardation values for the normal group were significantly higher than for those that showed proteoglycan infiltration ($p <$ 0·05). For both curves the minimum retardation occurred in the pure glycerol solution, corresponding to a refractive index of 1·46, which agrees with the findings of others on tendon collagen[15 21 22] and also with findings from studies of myocardial scar

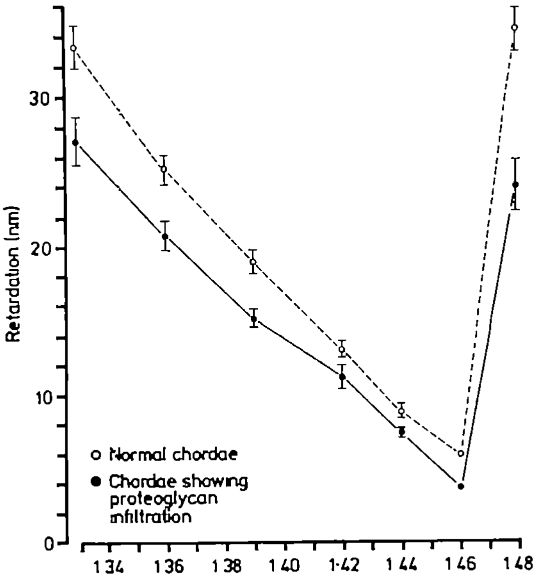

Fig 1 *Combined form birefringence curves for collagen sections from normal chordae tendineae and those with proteoglycan infiltration. Where it is large enough the standard error of the mean is shown.*

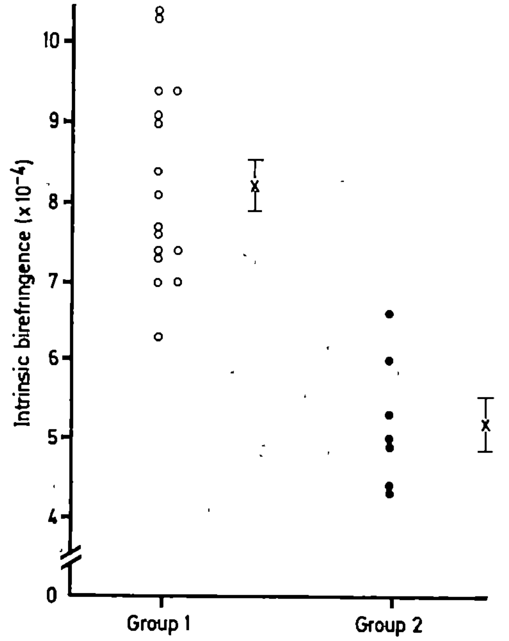

Fig 2 *The intrinsic birefringence of the collagen from the normal chordae (group 1) and those showing proteoglycan infiltration (group 2). Mean (SE) is shown for both groups. The intrinsic birefringence was significantly higher ($p < 0{\cdot}001$) in the normal tendons.*

and arterial collagen.[14] We used the minimum retardation to calculate (equation 1) the intrisic birefringence of the collagen in each of the chordae (fig 2). The average intrinsic birefringence of the abnormal chordae was significantly lower ($p < 0{\cdot}001$) than that of the normal chordae. Two chordae showed regions of collagen degradation when stained with picrosirius red—that is some of the fibres appeared green when viewed with polarised light. These regions had been deliberately avoided in the imbibition analysis measurements. Both of these chordae also had proteoglycan infiltration.

Figure 3 shows the correlation of the histological findings with the necropsy and surgical reports. Of the 16 chordae identified as having no evidence of proteoglycan infiltration, five were obtained at the time of replacement surgery and the remaining 11 were from necropsy samples. The surgical reports and the gross pathological descriptions of the surgical specimens from this group showed that three were from stenotic mitral valves and two were from valves with features compatible with floppy valves.

Of the seven chordae that showed proteoglycan infiltration, four were from surgical specimens all of which had been identified as floppy valves and the other three were from necropsy specimens. The pathological report on one of the latter described the specimen as being a floppy valve.

In summary, collagen in all of the sections with proteoglycan infiltration had lower intrinsic birefringence values than sections with no proteoglycan infiltration. This indicates that at the molecular level collagen in such sections is less organised than normal.

Discussion

We chose chordae tendineae rather than the mitral valve leaflets themselves for this study because collagen fibres in the chordae are highly aligned. In valve leaflets collagen fibre organisation is multidirectional. Since retardation is dependent on orientation it is difficult to ensure that the true retardation is measured when the fibres do not lie in the section plane.

Involvement of mitral chordae in the myxomatous process is known to be variable, and the finding of some normal chordae in patients with floppy valves is to be expected, especially since we were only able to obtain a single tendon from each valve. Also, localised myxomatous change has been found in otherwise unremarkable valves.[2 23]

The molecular organisation of the collagen in the chordae tendineae will influence their mechanical properties. The imbibition analysis technique was used to examine that molecular organisation. It is a well established technique in ultrastructure research[24] and in particular has been used to study the changes occurring in the molecular organisation of collagen in the healing and ageing of rat Achilles tendon.[21 25] The significantly lower intrinsic birefringence values of collagen in the chordae that showed proteoglycan infiltration indicated less molecular organisation in these chordae. There are

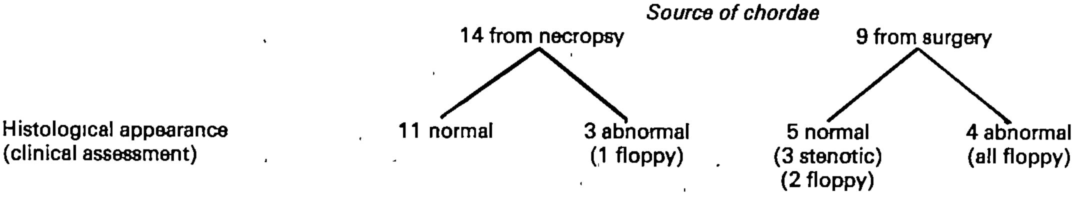

Fig 3 *Correlation of the histological findings on the chordae tendineae with the necropsy and surgical reports.*

several possible explanations for this. Firstly, the collagen in the abnormal chordae could be immature. Mello *et al* have shown that immature collagen has a lower intrinsic birefringence that normal collagen.[25] Thus our results could be interpreted to mean that the abnormal chordae were composed entirely of immature collagen. This seems unlikely because Doillon *et al* have shown that around 90 days of age maturing collagen attains retardation values comparable to those of mature collagen.[26] This would mean that the abnormal chordae were composed of collagen less than three months old. It is difficult to imagine how this situation could occur. The finding of Cole *et al* of increased production of collagen and glycosaminoglycans, plus cell proliferation in the valve,[27] does, however, suggest that a repair process is occurring. A repair process might be associated with the presence of immature collagen and this could be partially responsible for the lower intrinsic birefringences observed. Immature collagen is more extensible and weaker than mature collagen[26 28]; therefore, its presence might enable the valve leaflets to prolapse into the atrium.

The second possible explanation is that the altered intrinsic birefringence was due to collagen degradation. This would also lead to increased extensibility and a decrease in the tensile strength. In vivo such a change could result in increased chordal strain at any given stress, causing the chordae to lengthen and the valve cusps to prolapse into the atrium. With extensive collagen degradation, chordal rupture could occur. Obvious collagen degradation was seen in only two of the abnormal samples when they were stained with picrosirius red, but since this method is dependent on collagen fibre diameter[18] it may not be able to detect the early stages of degradation.

The third possible explanation, and the one that appears most plausible, is that the initial degradation does not involve the collagen per se but rather represents the removal of ground substance bound to the collagen fibre. It has been shown that proteoglycans are bound by collagen fibres in an organised manner, which contributes to the birefringence.[15 22] Therefore, if the ground substance is removed from the collagen the intrinsic birefringence would decrease. The proteoglycan "pools" characteristic of myxomatous infiltration could be regions in which the removed proteoglycans accumulate. Removal of ground substance bound to the collagen could also explain the difference in the shape of the form birefringence curves. The slope of the curve for the normal chordae was steeper than that for the abnormal chordae. Although further experiments would be required to determine the importance of these changes, the shape of the curve for the abnormal chordae is similar to those reported by Vidal, who used enzymes to remove bound ground substance from normal rat Achilles tendons.[22] Ground substance is known to play an important role in the mechanical properties of tendons.[29] Treatment of human Achilles tendon with α amylase (which removes structural glycoproteins from collagen) has been found to cause a substantial reduction (up to 38%) in breaking strength and an increase in extensibility.[30] In chordae tendineae, this effect would allow the chordae to extend and the valve cusps to prolapse.

In summary, our results indicate that, although proteoglycan infiltration may not be a specific marker for floppy valves, its presence is associated with evidence of degradation of the collagenous matrix. This finding agrees with the opinion of King *et al*[2] and suggests that the extent of valvar involvement in this process is likely to be a major factor in determining the functional effect. It is yet to be determined whether it is the collagen itself that is degraded or whether it is the ground substance that is removed from the collagen. The polarised light technique of imbibition analysis provided data not obtainable by the scanning electron microscopy studies that have been used to investigate the ultrastructure of floppy mitral valves.

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References

1 Read RI, Thal AP, Wendt VE. Symptomatic valvular myxomatous transformation (the floppy valve syndrome). A possible forme fruste of the Marfan syndrome. *Circulation* 1965;**32**:897–910.

2 King BD, Clark MA, Baba N, Kilman JW, Wooley CF. "Myxomatous" mitral valves: collagen dissolution as the primary defect. *Circulation* 1982;**66**:288–96.

3 Simpson JW, Nora JJ, McNamara DG. Marfan's syndrome and mitral valve disease: acute surgical emergencies. *Am Heart J* 1969;**77**:96–9.

4 Leier CV, Call TD, Fulkerson PK, Wooley CF. The spectrum of cardiac defects in the Ehlers-Danlos syndrome, Types I and III. *Ann Intern Med* 1980;**92**:171–8.

5 Hammer D, Leier CV, Baba N, Vasko CF, Wooley CF, Pinnell SR. Altered collagen composition in a prolapsing mitral valve with ruptured chordae tendineae. *Am J Med* 1979;**67**:863–6.

6 Lee YS, Lee AH, Lu AH, *et al* Biochemical analysis and electron microscopy of human mitral valve collagen in patients with various etiologies of mitral valve disease. *Jpn Heart J* 1983;**24**:529–38

7 Henney AM, Parker DJ, Davies MJ. Collagen biosynthesis in normal and abnormal human heart valves. *Cardiovasc Res* 1982;**16**:624–30.

8 Caulfield JB, Page DL, Kastor JA, Sanders CA. Connective tissue abnormalities in spontaneous rupture of chordae tendineae. *Arch Pathol* 1971;**91**:537–41.

9 Scott-Jupp W, Barnett NL, Gallagher PJ, Munro JL, Ross JL. Ultrastructural changes in spontaneous rupture of mitral valve chordae tendineae. *J Pathol* 1981;**133**:185–201.

10 Guthrie RB, Edwards JE. Pathology of the myxomatous mitral valve. *Minn Med* 1976;**59**:637–47.

11 Lim KO, Boughner DR. Mechanical properties of human mitral valve chordae tendineae: variation with size and strain rate. *Can J Physiol Pharmacol* 1975;**53**:330–9.

12 Bennett HS. The microscopical investigation of biological materials with polarized light. In. McClung-Jones R, ed. *McClung's handbook of microscopical technique*. New York: PB Hoeber, 1950:591–677.

13 Bendet IJ, Bearden I. Birefringence of spermatozoa. *J Cell Biol* 1972;**55**:501–10.

14 Whittaker P. Structural analysis of cardiovascular tissue using quantitative polarised light microscopy. University of Western Ontario, 1986. Ph.D. Thesis.

15 Vidal BC. The part played by proteoglycans and structural glycoproteins in the macromolecular orientation of collagen bundles. *Cell Mol Biol* 1980;**26**:415–21.

16 Sweat F, Puchtler H, Rosenthal SI. Sirius red F3BA as a stain for connective tissue. *Arch Pathol* 1964;**78**:69–72.

17 Junqueira LCU, Bignolas G, Bretani R. Picrosirius staining plus polarizing microscopy, a specific method for collagen detection in tissue sections. *Histochem J* 1979;**11**:447–55.

18 Junqueira LCU, Montes GS, Sanchez EM. The influence of tissue section thickness on the study of collagen by the picrosirius-polarization method. *Histochemistry* 1982;**74**:153–6.

19 Perez-Tamayo R, Montfort I. The susceptibility of hepatic collagen to homologous collagenase in human and experimental cirrhosis of the liver. *Am J Pathol* 1980,**100**·427–40.

20 Junqueira LCU, Zugaib M, Montes GS, Toledo OMS, Krisztan RM, Shigihara RM. Morphology and histochemical evidence for the occurrence of collagenolysis and for the role of neutrophilic polymorphonuclear leukocytes during cervical dilation. *Am J Obstet Gynecol* 1980;**138**:273–81

21 Mello MLS, Vidal BC, de Carvalho AC, Caseior-Filho AC. Change with age of anisotropic properties of collagen bundles. *Gerontology* 1979;**25**:2–8.

22 Vidal BC. The part played by the mucopolysaccharides in the form birefringence of collagen. *Protoplasma* 1965;**59**·472–9

23 Malcolm AD. Mitral valve prolapse associated with other disorders: casual coincidence, common link, or fundamental genetic disturbance? *Br Heart J* 1985;**53**:353–62.

24 Frey-Wyssling A. Ultrastructure research in biology before the electron microscope *J Microsc* 1974,**100**:21–34.

25 Mello MLS, Godo C, Vidal BC, Abujadi JM Changes in the macromolecular orientation of collagen fibres during the process of tendon repair in the rat. *Ann Histochem* 1975;**20**:145–52.

26 Doillon CJ, Dunn MG, Bender E, Silver FH Collagen fiber formation in repair tissue: development of strength and toughness. *Collagen Relat Res* 1985;**5**:481–92.

27 Cole WG, Chan D, Hickey AJ, Wilcken DEL. Collagen composition of normal and myxomatous human mitral heart valves. *Biochem J* 1984;**219**.451–60.

28 Gillman T. On some aspects of collagen formation in localized repair and in diffuse fibrotic reactions to injury. In: Gould BS, ed. *Treatise on collagen*. Vol. 2, part B. New York: Academic Press, 1968:331–407.

29 Viidik A, Danielson CC, Oxlund H. On fundamental and phenomenological models, structure and mechanical properties of collagen, elastin and glycosaminoglycan complexes. *Biorheology* 1982;**19**:437–51.

30 Minns RJ, Soden PD, Jackson DS. The role of fibrous components and groundsubstance in the mechanical properties of biological tissue: preliminary investigation. *J Biomech* 1973;**6**:153–65.

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Treatment of primary pulmonary hypertension with intravenous epoprostenol (prostacyclin)

D KEVIN JONES,[†] TIM W HIGENBOTTAM,[†] JOHN WALLWORK[*]

From the Departments of Surgery[*] and Respiratory Physiology,[†] Papworth Hospital, Papworth Everard, Cambridge

SUMMARY Ten patients with severe primary pulmonary hypertension and pronounced disability who were unresponsive to oral vasodilators were treated with intravenous epoprostenol (prostacyclin). All had been referred for heart and lung transplantation. Short term administration of epoprostenol (mean dose 5·5 ng/kg/min) increased the mean cardiac index from 1·8 to 2·2 l/min/m^2, improved pulmonary artery oxygen saturation from 48% to 57%, and increased calculated tissue oxygen delivery from 10 to 11·8 ml/kg/min. The mean pulmonary vascular resistance fell by 18% while mean systemic artery pressure fell by 32%. Pulmonary artery pressure rose in only two patients. Continued intravenous infusion of epoprostenol for 1–25 months was associated with subjective and clinical improvement. Exercise tolerance improved as measured by an increase in the maximum rate of oxygen consumption during progressive exercise testing. In those six patients who were able to exercise before treatment it rose from a mean of 7 to 15 ml/kg/min. Those who had been unable to exercise before treatment achieved comparable rates of oxygen consumption after treatment. Two patients died on treatment, three have undergone heart-lung transplantation, and in five the treatment is continuing. Complications included episodes of septicaemia and ascites.

In this uncontrolled study of patients with severe pulmonary hypertension epoprostenol seemed to offer a means of optimally dosing the patients with a vasodilator to reduce pulmonary vascular resistance and thus increasing cardiac output and oxygen tissue delivery. There was no evidence to suggest that this treatment influenced the progress of the disease.

Primary pulmonary hypertension is defined as pulmonary arterial hypertension of unknown cause,[1] and has been shown to be associated with three distinct pulmonary diseases[2]: pulmonary veno-occlusive disease, which can have characteristic clinical features,[3] so called recurrent thromboembolism; and plexogenic arteriopathy. Most clinicians regard plexogenic pulmonary arteriopathy as true primary pulmonary hypertension but it can be difficult to distinguish this disease from thrombotic pulmonary hypertension on the basis of clinical or haemodynamic variables.[4] Primary pulmonary hypertension has a poor prognosis and no treatment has been shown to reverse its progress.[5]

Oral vasodilator treatment can reduce the increased pulmonary vascular resistance and increase the low cardiac output characteristic of the disease,[6 7] and sustained clinical improvement has been reported in a small proportion of patients. Such treatment can also produce severe and refractory systemic hypotension.[8 9]

An intravenous infusion of epoprostenol (prostacyclin) induced short term pulmonary vasodilatation in primary pulmonary hypertension.[10] Because of its short half life, the dose can be titrated to produce a desired haemodynamic effect and any adverse effects are reversed immediately by discontinuing the infusion. It is a safe agent to use for the initial testing of a patient's responsiveness to a vasodilator[10] but it has not been used on a long term basis because no oral preparation is available. We have previously shown that long term treatment of primary pulmonary hypertension can be achieved

Requests for reprints to Dr Tim W Higenbottam, Department of Respiratory Physiology, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE.

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Table 1 *Data on 10 patients with primary pulmonary hypertension*

Patient	*Sex*	*Age (yr)*	*Duration of symptoms (months)*	*Time since diagnosis (months)*	*Clinical severity of disability*	*Drug treatment*		*Biopsy specimen*
1	F	28	78	8	Confined to hospital ward	Spironolactone	100 mg daily	Plexogenic arteriopathy
						Frusemide	160 mg daily	
						Continuous oxygen		
						Warfarin		
2	F	38	16	12	Confined to hospital ward	Digoxin		Thrombotic pulmonary hypertension
						Spironolactone	100 mg daily	
						Frusemide	80 mg daily	
						Bendrofluazide	5 mg daily	
						Oxygen	18 h/day	
						Warfarin		
3	F	21	14	10	Unable to walk 300 m	Warfarin		Thrombotic pulmonary hypertension
4	F	38	60	4	Unable to walk 200 m	Bumetanide	2 mg daily	Plexogenic arteriopathy
						Oxygen at night		
						Warfarin		
5	F	39	12	2	Unable to climb one flight of stairs	Nil		Plexogenic arteriopathy
6	M	24	16	1·5	Unable to walk 100 m	Digoxin		NA
						Warfarin		
						Cyclopenthiazide	0·1 mg daily	
7	M	17	23	3	Confined to a wheelchair	Digoxin		NA
						Disopyramide		
						Warfarin		
8	F	32	48	40	Confined to a wheelchair	Oxygen		NA
						Digoxin		
						Frusemide	80 mg daily	
						Warfarin		
9	M	34	5	1	Unable to walk 300 m	Warfarin		NA
10	M	32	31	27	Unable to walk 50 m	Frusemide	80 mg daily	Thrombotic pulmonary hypertension
						Amiloride	10 mg daily	
						Warfarin		

NA, not available.

with intravenous epoprostenol[11] and we now report on the successes, problems, and failures of this treatment in ten patients, including our original patient.

Patients and methods

PATIENTS

Ten patients diagnosed as having primary pulmonary hypertension were seen at our unit between November 1982 and January 1985. The six women and four men (mean age 30 years) had had symptoms for an average of 30 months and the mean time since diagnosis was 6 months. All were severely disabled by breathlessness and fatigue. Table 1 shows details of the individual patients. Five patients had suffered syncopal episodes, two had angina on minimal exertion, and all but patients 5 and 7 had clinical signs of right ventricular failure. The diagnosis of primary pulmonary hypertension had been reached in each patient after the exclusion of other causes of pulmonary hypertension by chest radiography, pulmonary function testing, echocardiography, isotope ventilation-perfusion imaging, and cardiac catheterisation. All except patients 4 and 8 had undergone pulmonary angiography and in each case this had been reported as showing no evidence of major vessel thromboembolism. Patient 8 had normal ventilation perfusion lung scans. In six patients histological material was examined. Patients 4, 5, and 10 underwent open lung biopsy, and later patients 1, 3, and 5 had both lungs removed during heart-lung transplantation. A necropsy was performed on patient 2.

All patients but one were receiving oral anticoagulants, six were taking diuretics, four were taking digoxin, and four required oxygen. All patients had received a trial of treatment with at least one vasodilator. The methods for assessing response had varied (table 2) but no patient had reported subjective improvement while taking oral vasodilators.

All patients were referred to our unit to be considered for heart-lung transplantation because of their poor clinical condition, which had worsened despite treatment. Table 3 shows data collected by their referring physicians 1–18 (mean 5·5) months before catheterisation at our unit. Not all the measured

Table 2 *Details of previous vasodilator treatment and its effect*

Patient	*Drug*	*Daily dose (mg)*	*Route*	*Duration*	*Effect*
1	Hydralazine Nifedipine Isosorbide	50 60 20	Oral Oral Oral	2 days 6 weeks 6 weeks	Stopped due to syncope No subjective improvement No subjective improvement
2	Nifedipine Diazoxide	10 300	Oral Into PA	1 dose 1 dose	No reduction in PVR No reduction in PVR
3	Hydralazine Nifedipine	50 30	Oral Oral	1 day 4 weeks	Stopped due to nausea No subjective improvement
4	Glyceryl trinitrate Nifedipine Nifedipine	0·5 10 60	Sublingual Oral Oral	1 dose 1 dose 4 weeks	Reduced PVR by 37% Reduced PVR by 12% No subjective improvement
5	Hydralazine	400	Oral	4 weeks	No increase in exercise tolerance Caused eosinophilia
6	Diazoxide Diazoxide	150 300	Oral Oral	1 dose 1 day	No reduction in PVR Stopped due to syncope
7	Captopril	150	Oral	18 weeks	No subjective improvement
8	Pirbuterol Pirbuterol	15 45	Oral Oral	1 dose 13 weeks	No reduction in PVR No subjective improvement
9	Nifedipine	30	Oral	4 weeks	No subjective improvement
10	Captopril	150	Oral	10 weeks	No objective increase in exercise tolerance

PA, pulmonary artery, PVR, pulmonary vascular resistance

variables were determined in every patient, but the available data showed a deterioration in their pulmonary vascular resistance (PVR) and pulmonary arterial oxygen saturation (Pao_2 saturation) and a significant rise in the mean pulmonary arterial pressure (PAP). This supports the clinical observation that the patients' conditions were rapidly deteriorating.

HAEMODYNAMIC MEASUREMENTS

The effect of short term administration of epoprostenol was assessed in each patient after we stopped anticoagulant treatment and obtained written informed consent. A triple lumen flow directed catheter was used to perform right heart catheterisation in a supine patient. Mean right atrial, pulmonary-arterial, and pulmonary arterial wedge pressures (RAP, PAP, and PAWP) were obtained by electronic integration of the pressure signals with the midaxillary line as the zero reference level. Mean systemic arterial pressure (SAP) and heart rate (HR) were monitored continuously via a radial artery cannula and electrocardiograph. Radial arterial oxygen saturation and pulmonary arterial oxygen saturation were determined by a blood gas analyser (ABL 3 Radiometer, Copenhagen, Denmark) and cardiac output (CO) by thermodilution and a bedside cardiac output computer (American Edwards Laboratories, Santa Ana, California, USA). The following formulas were used to calculate further indices.

Cardiac index (CI) = CO surface area ($l/min/m^2$)

Pulmonary vascular resistance (PVR) =

$$\frac{\text{mean PAP} - \text{mean PAWP}}{\text{CO}} \times 80\,(\text{dyn s cm}^{-5})$$

Systemic vascular resistance (SVR) =

$$\frac{\text{mean SAP} - \text{mean RAP}}{\text{CO}} \times 80\,(\text{dyn s cm}^{-5})$$

O_2 content =

$$\frac{O_2\ \text{saturation} \times O_2\ \text{capacity}}{100} + \text{dissolved } O_2$$

where O_2 capacity = Hb (g/dl) × 1·36

Peripheral O_2 delivery =

arterial O_2 content × CO (ml/min)

Epoprostenol (Flolan) was supplied by Wellcome Foundation Ltd (Beckenham, Kent) as the sodium salt and made up for infusion in a sterile glycine buffer. After baseline measurements had been obtained it was administered as an initial infusion of 2 ng/kg/min through a peripheral vein. The dosage

Table 3 *Haemodynamic data (mean (SEM)) at previous catheterisation compared with measurements at our unit. (Figures in parentheses are the numbers of patients in which the individual measurements were compared)*

	Previous catheterisation	*Our catheterisation*	*P value*
PAP (10) (mm Hg)	66 (6)	76 (6)	<0·02
PVR (6) (dyn s cm^{-5})	1354 (200)	1634 (225)	<0·005
Pao_2 (5) saturation(%)	62 (2)	49 (3)	<0·001
CI (5) ($l/min/m^2$)	2·2 (0·2)	1·8 (0·2)	<0·005

PAP, pulmonary artery pressure, PVR, pulmonary vascular resistance, Pao_2, pulmonary arterial oxygen saturation; CI, cardiac index.

was increased by 1 ng/kg/min every 15 minutes and the haemodynamic measurements were repeated before each dose increment. The protocol was continued until a significant (20%) change in pulmonary vascular resistance or systemic arterial pressure was observed or side effects occurred.

LONG TERM TREATMENT

After the short term trial the patients were started on long term intravenous treatment. A cannula (149 Nutricath no 218.20, Vygon UK Ltd, Cirencester) was inserted through a subcutaneous tunnel into a subclavian vein and connected via a length of sterile manometer tubing and a three way stopcock to a 20 ml syringe containing the infusion. This was protected from light and administered continuously by a battery driven syringe pump with an automatic auditory alarm (MS16A, Graseby Dynamics, Bushey, Hertfordshire). The pump was carried in a small shoulder holster and the infusion system did not restrict the patients' mobility. The patients were taught how to prepare, store, administer, and maintain the infusion themselves so that they could live independently at home.

ASSESSMENT OF RESPONSE TO TREATMENT

The long term infusion was started at the maximal dose that had been comfortably tolerated during the short term trial. The patients' subjective feelings of well-being and their exercise tolerance were assessed during treatment. Clinical signs and the need for concomitant drug treatment were regularly reviewed. Patients had formal exercise testing before the start of epoprostenol treatment, if they were well enough, and at convenient intervals after start of the long term infusion. This consisted of walking on the level on a heavy duty electrically driven treadmill. The speed was increased by 0 9 km/h every minute until the patient felt unable to continue. At rest and then during the test oxygen consumption was calculated for each minute by measuring the partial pressure of mixed expired oxygen with a mass spectrometer and the total volume expired was measured with a pneumotachograph.[12] The maximum walking speed (WS) attained in km/h and the maximum oxygen consumption attained in ml/kg/min ($\dot{V}$ Max O_2) were recorded.

In an attempt to obtain maximum clinical benefit seven of the patients had one or more dosage increments during their long term treatment. Each increase was achieved during a period of hospital admission in which the systemic blood pressure was closely monitored.

The paired *t* test was used for statistical analysis of recorded data before and after intervention.

Results

SHORT TERM EFFECTS OF EPOPROSTENOL

The baseline measurements confirmed the presence of severe pulmonary hypertension in the 10 patients. Mean pulmonary artery pressure and pulmonary

Table 4 *Values for haemodynamic data at baseline and during maximal dose infusion during short term epoprostenol trial*

Patient	*Max dose of epoprostenol*	*SAP (mm Hg)*	*PAP (mm Hg)*	*CI ($l/min/m^2$)*	*PVR (dyn s cm^{-5})*	*SVR (dyn s cm^{-5})*	*HR (beats/min)*	*Pao_2 saturation*	*o_2 delivery (ml/kg/min)*
1	Baseline	78	100	1 7	2133	1600	104	45	5 8
	4 ng/kg/min	77	81	2 3	1190	1200	120	50	8 2
2	Baseline	82	71	1 5	1899	1992	70	38	—
	6 ng/kg/min	66	68	1 9	1365	1223	82	45	—
3	Baseline	80	55	1·7	1376	1952	98	52	10 9
	5 ng/kg/min	65	65	1 8	1629	1425	104	53	11 9
4	Baseline	83	80	2 1	1558	1684	87	60	9 5
	4 ng/kg/min	75	80	2 6	1242	1174	90	70	11 6
5	Baseline	73	62	3 0	784	1094	90	51	15 2
	4 ng/kg/min	72	48	3 1	580	1020	90	61	16·8
6	Baseline	93	60	1 5	1583	2187	77	42	8 5
	6 ng/kg/min	80	60	1·8	1358	1457	84	56	9 5
7	Baseline	100	80	1 8	1800	2275	78	51	12 4
	6 ng/kg/min	80	80	2 1	1516	1579	82	57	14 3
8	Baseline	70	50	2 2	869	1440	63	60	11·8
	6 ng/kg/min	61	48	2 8	675	1031	68	68	15 1
9	Baseline	95	105	1 5	2744	2425	84	43	8 3
	8 ng/kg/min	70	105	2 0	2054	1340	96	57	10 9
10	Baseline	76	93	1 3	2523	1723	82	42	7 3
	6 ng/kg/min	62	98	1·45	2400	1048	82	51	8 1
Mean	Baseline	83 (3)	76 (6)	1 83 (0 2)	1727 (202)	1837 (129)	83 (4)	48 (2)	10 0 (1)
(SEM)	5 5 ng/kg/min	71 (2)	73 (6)	2 19 (0·2)	1401 (175)	1250 (61)	90 (4)	57 (2)	11 8 (1)
p value		<0 001	>0 4	<0 005	<0 02	<0 001	<0·005	<0 001	<0 001

SAP, systemic arterial pressure, PAP, pulmonary artery pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; HR, heart rate; Pao_2 sat, pulmonary arterial oxygen saturation, o_2 delivery, peripheral oxygen delivery.

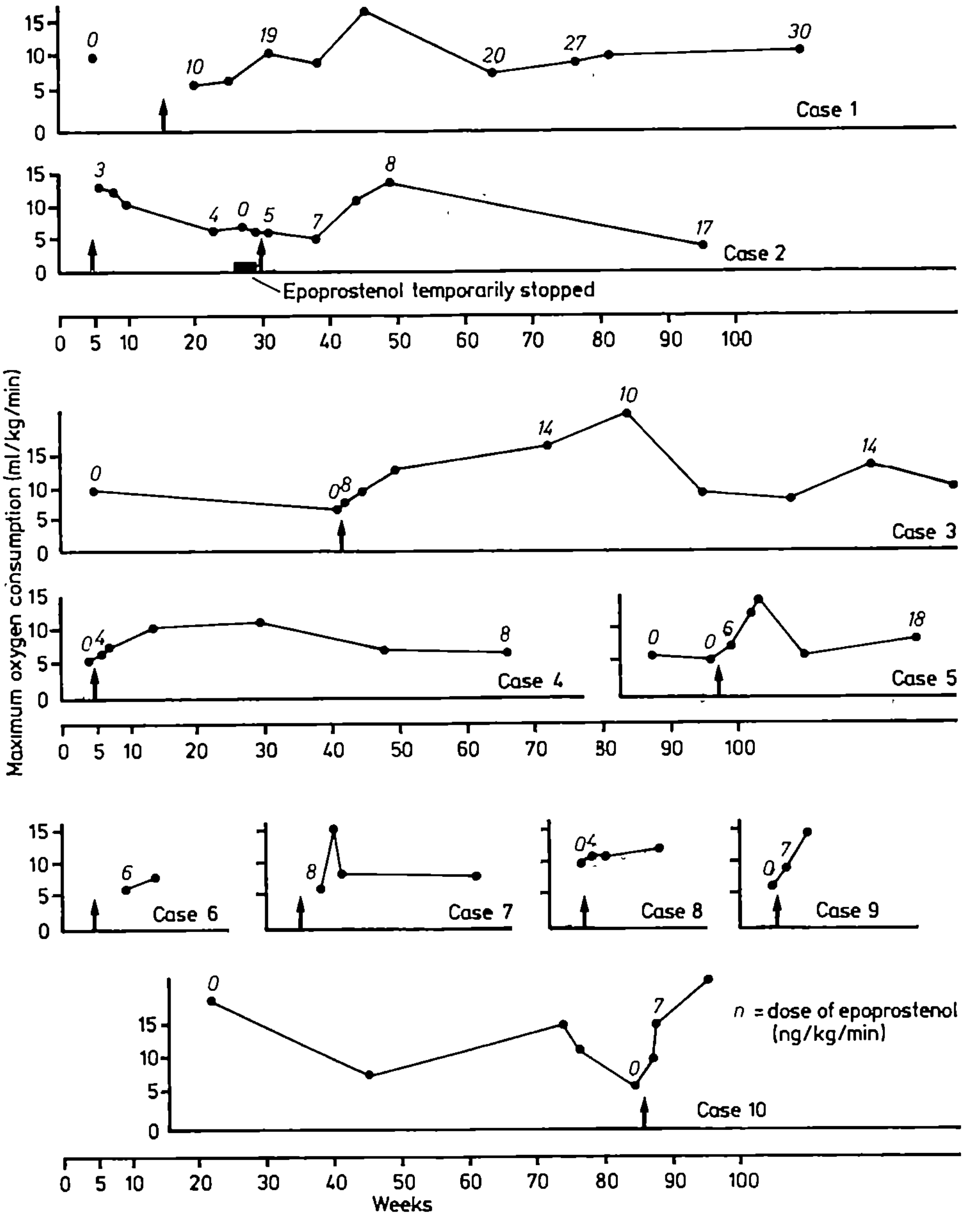

Fig 1 *Individual exercise tolerances expressed as maximum oxygen consumption at various times before and after starting epoprostenol.* ↑ *Epoprostenol started.*

vascular resistance were high and cardiac index and pulmonary arterial oxygen saturation were low (table 4). There was a significant fall in pulmonary vascular resistance after epoprostenol. This was small and of doubtful physiological significance in four and large in three. There was a statistically significant decrease in the mean systemic arterial pressure and systemic vascular resistance and a statistically significant rise in the mean cardiac index. Mean pulmonary arterial oxygen saturation rose from 48% to 57% and the mean peripheral oxygen delivery from 10 to 11·8 ml/kg/min. There was a

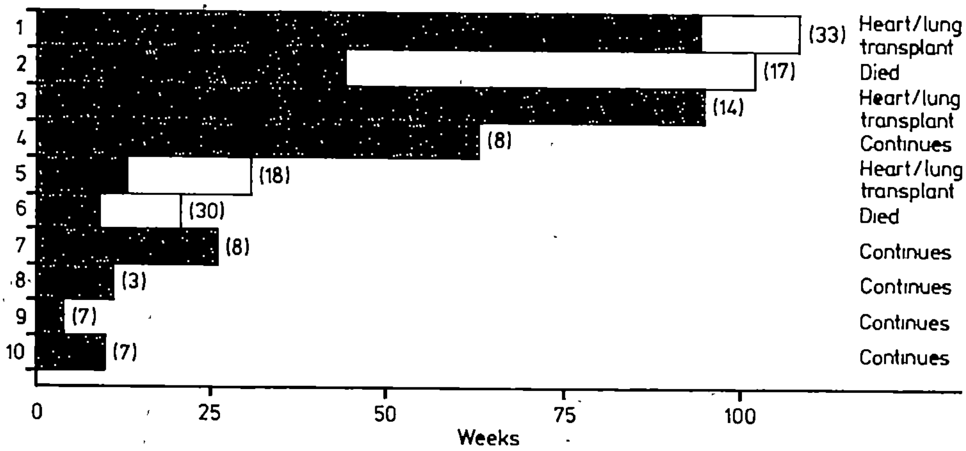

Fig 2 *Duration of epoprostenol treatment and subjective effects of epoprostenol and final outcomes in individual patients. Length of time that subjective benefit was present is indicated by cross hatching. Numbers in parentheses show maximum dose of epoprostenol (ng/kg/min).*

small increase in mean heart rate during the infusion but no change in pulmonary arterial wedge or right atrial pressures. The mean falls in pulmonary vascular and systemic vascular resistances were 19% and 32% respectively. In only two patients (1 and 5) was the fall in pulmonary vascular resistance greater than the fall in systemic vascular resistance.

EFFECTS OF LONG TERM EPOPROSTENOL

All but patient 9 noted a subjective improvement in well-being and exercise tolerance within a week of starting long term treatment. The subjective benefit was confirmed on formal exercise testing (fig 1). Four patients were too ill to exercise before epoprostenol but after long term treatment they reached a mean walking speed (SEM) of 4 (0·6) km/h and a mean maximum oxygen consumption of 13·4 (2·0) ml/kg/min. The six patients who exercised shortly before starting epoprostenol increased their mean walking speed from 2·5 (0·7) to 4·3 (0·6) km/h ($p < 0·01$) and their maximum oxygen consumption from 7·2 (0·7) to 14·9 (1·4) ml/kg/min ($p < 0·01$). All patients showed an initial improvement in exercise performance during epoprostenol treatment. Figure 1 shows that individual exercise performances continued to improve or were sustained in some patients while in others improvement was only temporary. Subjective benefit was held to be present if the patients reported improved symptoms and exercise tolerance that worsened within 30 minutes of the infusion being interrupted.

CLINICAL PROGRESS

Figure 2 shows that five patients have felt better on epoprostenol for over 24 weeks to 2 years.

All patients (except patient 6) initially were able to leave hospital and return home to an improved quality of life. Three of the patients have since undergone heart-lung transplantation. Patients 1 and 3 remained well on the infusion until short periods of deterioration prompted operation. Patient 5 did well initially but then suffered two episodes of septicaemia, the second of which was associated with a cardiorespiratory arrest. She slowly recovered and subsequently had a heart-lung transplant.

After initial improvement patient 6 had a relapse into refractory right ventricular failure after a cardiorespiratory arrest during follow up cardiac catheterisation. This event was not associated with any change in epoprostenol dosage and appeared to occur during repositioning of the catheter. Recurrent massive ascites and renal failure developed and the patient died five months after starting treatment. After an impressive initial response, patient 2 slipped back to her previous condition. The infusion was stopped for a short time and reintroduction of epoprostenol at a higher dose was associated with a further impressive response. After 10 months' treatment, however, she relapsed into gross right ventricular failure which was unresponsive to an increasing dose of epoprostenol.

The other five patients have received epoprostenol for a comparatively short time but all report sustained benefit.

SIDE EFFECTS OF LONG TERM TREATMENT

In three patients septicaemia developed from infection at the tip of the indwelling cannula. In each case this was associated with a deterioration in well-being and exercise ability. In patients 1 and 3 it responded quickly to intravenous antibiotics and replacement of the intravenous cannula. In patient 5 two courses of antibiotics and resiting of the subclavian cannula did not eradicate the infection. Epoprostenol had to be given through a peripheral vein until the infection was controlled; then a further subclavian line was inserted.

Sterile ascites developed in three patients during long term treatment. In each case the fluid was straw coloured and contained a predominance of lymphocytes. The glucose and amylase concentrations of the fluid were normal but in each case the total protein content was > 35 g/l and electrophoresis showed a protein leak which was non-selective according to the results of molecular weight determinations. No patient had a raised erythrocyte sedimentation rate at diagnosis and in two of the patients tested antinuclear factor, DNA binding, and rheumatoid factor were not detected in the peripheral blood. Liver function tests showed a slight increase in aspartate aminotransferase concentrations. Patient 1 had normal computed tomographs of the liver and abdomen.

In patient 1 the ascites did not recur after paracentesis. In patient 2 it became massive and required repeated aspiration. In patient 6 it was massive, recurrent, and became chylous shortly before death. In all three patients the ascites was greater than would be expected from right ventricular failure alone and was not associated with generalised fluid retention of the same magnitude.

Higher doses of epoprostenol were tolerated by the patients than by normal volunteers. This was achieved without the commonly reported side effects of headache, flushing, and abdominal pain.[13] When these side effects did occur they were associated with an increase in the infusion dose but they were transient in nature, and normally subsided within 24 hours. We learnt to control side effects by increasing the infusion rate more gradually. In general the patients managed their treatment with very few problems. Five patients experienced sudden interruptions in their infusions; one because of pump failure, one because the line became disconnected, and three because they inadvertently turned off the pump. All noticed a considerable increase in symptoms within minutes and a prompt improvement when the infusion was restarted.

PATHOLOGICAL EXAMINATION

Histological specimens obtained in six patients showed medial hypertrophy of the pulmonary arterioles with widespread fibrocellular proliferation of the intima of all arteries and arterioles. In patients 1, 4, and 5 the changes were typical of plexiform pulmonary arteriopathy but in patients 2, 3, and 10 the vascular changes were associated with the presence of thrombi in peripheral pulmonary arteries. Patient 5 had an open lung biopsy before epoprostenol and both lungs were available for examination after heart-lung transplantation. There was no difference in the severity of the vascular lesions between the two specimens.

Discussion

This paper is not the report of a clinical trial but rather the observations of the effect of a treatment on ten patients with a severe, potentially fatal condition. Nevertheless, we made several important observations based on the subjective and objective data. These patients were treated with epoprostenol because all had severe primary pulmonary hypertension with a high pulmonary artery pressure and pulmonary vascular resistance and low cardiac index. All had a pulmonary arterial oxygen saturation below 63%, which is associated with a three year survival rate of < 20%.[4] In all, the symptoms were becoming worse and this was confirmed by haemodynamic measurements, a fall in pulmonary arterial oxygen saturation between catheterisations, and in four a measured decline in exercise capacity and maximum oxygen consumption. None had responded to conventional oral vasodilators.

The rationale behind the use of vasodilators in primary pulmonary hypertension is that the histological features of the condition may represent an inappropriate constriction of the pulmonary vasculature.[14] In the early stages of the disease the vasoconstriction is labile and responsive to vasodilators but later it becomes fixed and irreversible.[15] Short term administration of vasodilators in primary pulmonary hypertension most commonly causes a decrease in the pulmonary and systemic vascular resistance and an associated increase in cardiac output with little or no effect on the pulmonary artery pressure.[16] These haemodynamic changes can be sustained with long term oral treatment and can be associated with clinical and subjective improvement in the patient's condition.[7 17] The administration of vasodilators with long half lives can also cause profound systemic hypotension that is resistant to treatment and can lead to death.[8 9] Epoprostenol is a powerful vasodilator when it is administered intravenously. It has a rapid onset of action that is dose dependent.[10] It has a short half life so any adverse reaction can be rapidly reversed by discontinuing the infusion. The optimal dose of the infusion can be determined during a single right heart catheterisation. Most studies can be completed in two hours which is a much shorter time than that required for fully testing orally administered drugs. When epoprostenol is administered as a long term infusion, fluctuations in the blood concentration due to variable bioavailability are avoided, thus making it ideally suited to treatment of critically ill patients. It is possible that the problem with oral vasodilators is the maintenance of adequate concentrations in the blood.

The effect of short term infusion of epoprostenol in our patients was similar to that reported previously.[10] Some workers have claimed that in order to establish a pulmonary vasodilatation effect, there should be a fall in pulmonary artery pressure and the pulmonary vascular resistance should decrease more than systemic vascular resistance.[16] Only two of our patients fulfilled these criteria. The cardiac output, however, improved with no rise in pulmonary artery pressure in all but two patients. This improved cardiac output was associated with concomitant increases in pulmonary-arterial oxygen saturation and peripheral oxygen delivery. The increase in cardiac output was achieved without a large increase in heart rate or a change in right atrial pressure, suggesting there was no important increase in right ventricular workload.

In assessing the effect of long term epoprostenol, the ideal would be to repeat haemodynamic measurements. Right heart catheterisation is not without complications,[18] however, and in primary pulmonary hypertension is associated with a significant morbidity and mortality[4] as we witnessed in patient 6. Also although our patients' recordings were stable during their catheterisations, there can be spontaneous variability of haemodynamic function in primary pulmonary hypertension.[19] Because the increase in cardiac output was the major effect of epoprostenol we monitored our patients' progress non-invasively by means of treadmill exercise testing. Measurement of symptom limited maximum oxygen consumption has been shown to correlate with the cardiac output in normal subjects[20] and patients with left heart failure.[21] A recent paper has recommended its use also in assessing the response to oral vasodilators in "obliterative pulmonary hypertension".[22] All our patients improved clinically and subjectively and all increased their maximum oxygen consumption during exercise. This indicated that their improvement in cardiac output during the short term was sustained by the long term infusion. We believe that the symptomatic benefit of long term epoprostenol was due to its ability to increase cardiac output and tissue oxygenation; this resembles the mechanism of action of a response to oral hydralazine in patients with primary pulmonary hypertension.[23 24] Exactly how the increase in cardiac output is achieved remains uncertain but even in the absence of a fall in pulmonary artery pressure it probably represents some decrease in the obstruction of the pulmonary vasculature.[25] The mechanism is analogous to that which operates when vasodilators are given to patients with left ventricular dysfunction when reduction in afterload is accompanied by an increase in cardiac output rather than a fall in systemic arterial pressure. In both instances a fall in systemic arterial pressure resulting from a fall in systemic vascular resistance is counteracted by reflex increase in stroke volume.

The reason why all our patients responded both in the short term and in the long term is probably because we were able to reach the optimum vasodilating dose with the epoprostenol infusion; this is much more difficult to achieve with oral vasodilators.

Even when a clinical diagnosis of primary pulmonary hypertension has been made after extensive investigations including pulmonary angiography, other studies of necropsy specimens have shown that up to 60% of patients have evidence of recurrent pulmonary thromboembolism.[4 14] This was also seen in three of our six patients in whom the results of histological examination were available (patients 2, 3, and 10). In all of them pulmonary angiograms had excluded major vessel obstruction. Their short term and long term responses were similar to those in patients with classic plexiform pulmonary arteriopathy. It could be argued that the thrombi occurred in situ; however, in our group of patients the sex ratio is not typical of the usually recognised condition.

Some evidence suggests that anticoagulation may prolong survival[4] but most physicians believe that anticoagulants are useful only in preventing the secondary thromboembolism associated with low cardiac output.[26] As well as being a vasodilator, epoprostenol is a powerful platelet antiaggregator and if abnormal platelet behaviour was important in the pathogenesis of primary pulmonary hypertension this effect might be an added benefit of the treatment. Tests of platelet function in patients on epoprostenol infusions, however, showed an "intra-infusion" rebound of platelet activation starting at 2–4 days, reaching a maximum at 6–10 days, and then levelling off.[27] No clinical complication of this enhanced platelet activation was seen in our patients. Nor have they been reported after short term infusions of epoprostenol for peripheral vascular disease. This phenomenon should be further explored, in particular with reference to clinical complications.

Epoprostenol had a positive clinical benefit in all our patients and all but one became mobile and went home. This improvement was achieved by treating the effects rather than the cause of primary pulmonary hypertension. Treatment did not reverse the underlying disease process as its effects were not sustained in all patients. The two patients who died had the lowest pulmonary arterial oxygen saturation at the outset. It had no effect on the pulmonary pathology of the one patient whose lungs were examined before and after epoprostenol and in whom stopping the infusion had caused a rapid deterioration in clinical condition.

Treatment with epoprostenol improved the quality of life and the exercise tolerance in patients with a severe deteriorating disease who had not been helped by oral vasodilators. We believe that despite the problems of maintaining an intravenous infusion and the expense, this is a treatment that can be used in patients awaiting heart-lung transplantation when there may be a long wait for a suitable donor. A formal controlled study will be necessary, however, if epoprostenol infusion is to be considered for more general use in less severely affected patients with primary pulmonary hypertension.

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References

1 Hatano S, Strasser T, eds. *Primary pulmonary hypertension: report on a WHO meeting.* Geneva: World Health Organisation, 1975.7

2 Edwards WD, Edwards JE. Clinical primary pulmonary hypertension. 3 pathologic types. *Circulation* 1977;**56**:884–8.

3 Rosenthal A, Vawter G, Wagenvoort CA. Intrapulmonary veno-occlusive disease. *Am J Cardiol* 1973;**31**.78–83.

4 Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation* 1984;**70**:580–7.

5 Honey M. Pulmonary hypertension. In: Weatherall DJ, Ledingham JG, Warrell DA, eds. *Oxford textbook of medicine.* Oxford: Oxford University Press, 1983, Vol II, 13. 241.

6 Klinke WP, Gilbert JAL Diazoxide in primary pulmonary hypertension. *N Engl J Med* 1980;**302**:91–2.

7 Rubin LJ, Peter RH. Oral hydralazine therapy for primary pulmonary hypertension. *N Engl J Med* 1980;**302**:69–73.

8 Packer M, Greenberg B, Massie B, Dash H. Deleterious effects of hydralazine in patients with pulmonary hypertension. *N Engl J Med* 1982; **306**:1326–31.

9 Buch J, Wennevold A Hazards of diazoxide in pulmonary hypertension. *Br Heart J* 1981;**46**:401–3.

10 Rubin LJ, Groves BM, Reeves JT, Frosolano M, Handel F, Cato AE. Prostacyclin-induced pulmonary vasodilation in primary pulmonary hypertension. *Circulation* 1982;**66**:334–8.

11 Higenbottam T, Wheeldon D, Wells F, Wallwork J. Long-term treatment of primary pulmonary hypertension with continuous intravenous epoprostenol (prostacyclin). *Lancet* 1984,**i**:1046–7.

12 Davies NJH, Denison DM. Measurement of metabolic gas exchange and minute volume by mass spectrometry alone. *Respir Physiol* 1979,**36**.261–7.

13 Pickles H, O'Grady J Side effects occurring during administration of epoprostenol (prostacyclin, PG12) in man *Br J Clin Pharmacol* 1982;**14**:177–85.

14 Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension. A pathologic study of the lung vessels in 156 clinically diagnosed cases. *Circulation* 1970; **42**:1163–84.

15 Samet P, Bernstein WH. Loss of reactivity of the pulmonary vascular bed in primary pulmonary hypertension. *Am Heart J* 1963;**66**.197–9

16 Rich S, Martinez J, Lam W, Levy PS, Rosen KM. Reassessment of the effects of vasodilator drugs in primary pulmonary hypertension guidelines for determining a pulmonary vasodilator response. *Am Heart J* 1983,**105**:119–27.

17 Rubin LJ, Nicod P, Hillis D, Firth BG. Treatment of primary pulmonary hypertension with nifedipine. A haemodynamic and scintigraphic evaluation. *Ann Intern Med* 1983;**99**:433–8.

18 Rowley KM, Coni Clubb K, Walker Smith GJ, Cabin S. Right sided infective endocarditis as a consequence of flow-directed pulmonary-artery catheterisation. A clinicopathological study of 55 autopsied patients *N Engl J Med* 1984,**311**:1152–6.

19 Rich S, Martinez J, Lam W, Rosen KM. Captopril as treatment for patients with pulmonary hypertension: problem of variability in assessing chronic drug treatment *Br Heart J* 1982;**48**:272–7.

20 Jones NL, Campbell EJM. *Clinical exercise testing.* London: WB Saunders, 1982:32–4.

21 Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilisation and ventilation during exercise in patients with chronic cardiac failure. *Circulation* 1982;**65**:1213–23.

22 D'Alonzo GE, Gianotti L, Dantzker DR. Non-invasive assessment of hemodynamic improvement during chronic vasodilator therapy in obliterative pulmonary hypertension. *Am Rev Respir Dis* 1986; **133**:380–4.

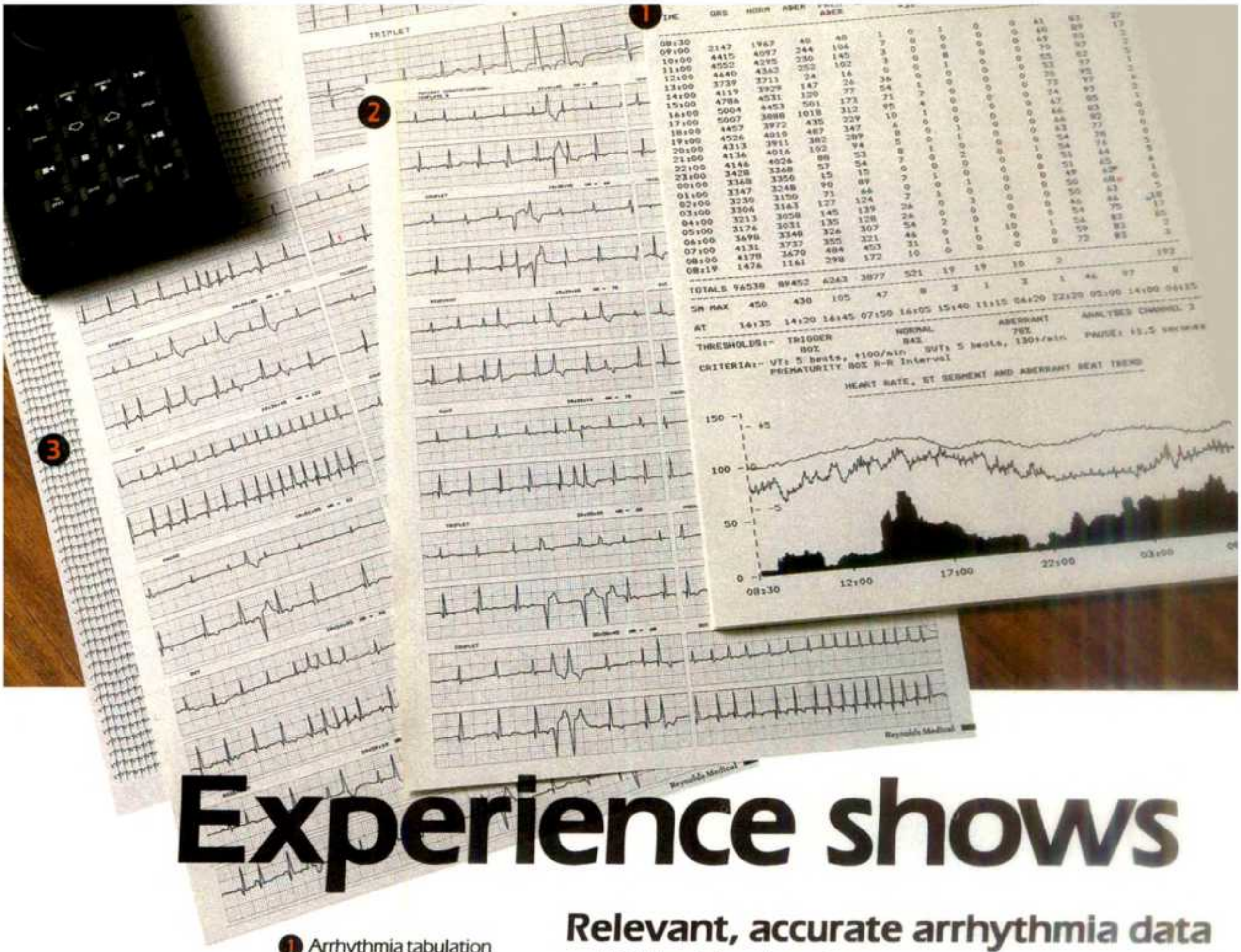
23 McGoon MD, Seward JB, Vlietstra RE, Choo MH, Moyer TP, Reeder GS. Haemodynamic response to intravenous hydralazine in patients with pulmonary hypertension. *Br Heart J* 1983,**50**:579–85.

24 Fishman AP. Unexplained pulmonary hypertension. *Circulation* 1982;**65**:651–2.

25 Reeves JT. Vasodilator therapy for pulmonary hypertension [Letter]. *N Engl J Med* 1980;**302**:1261–2.

26 Oakley CM. Management of primary pulmonary hypertension *Br Heart J* 1985;**53**:1–4.

27 Sinzinger H, Leithner C, Silberbauer K. Rebound platelet activation during continuous epoprostenol infusion. *Lancet* 1984,**ii**.759.



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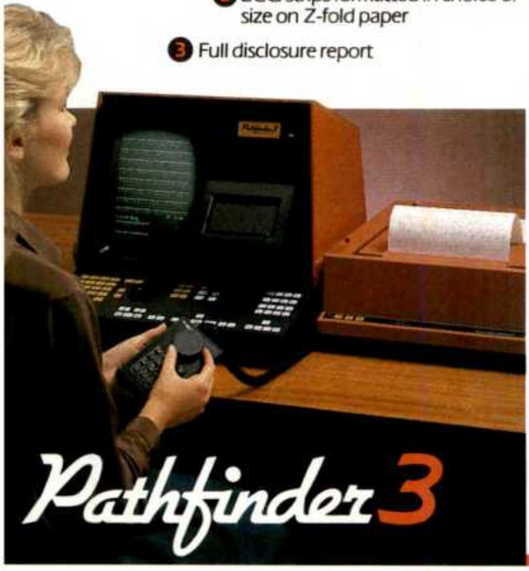

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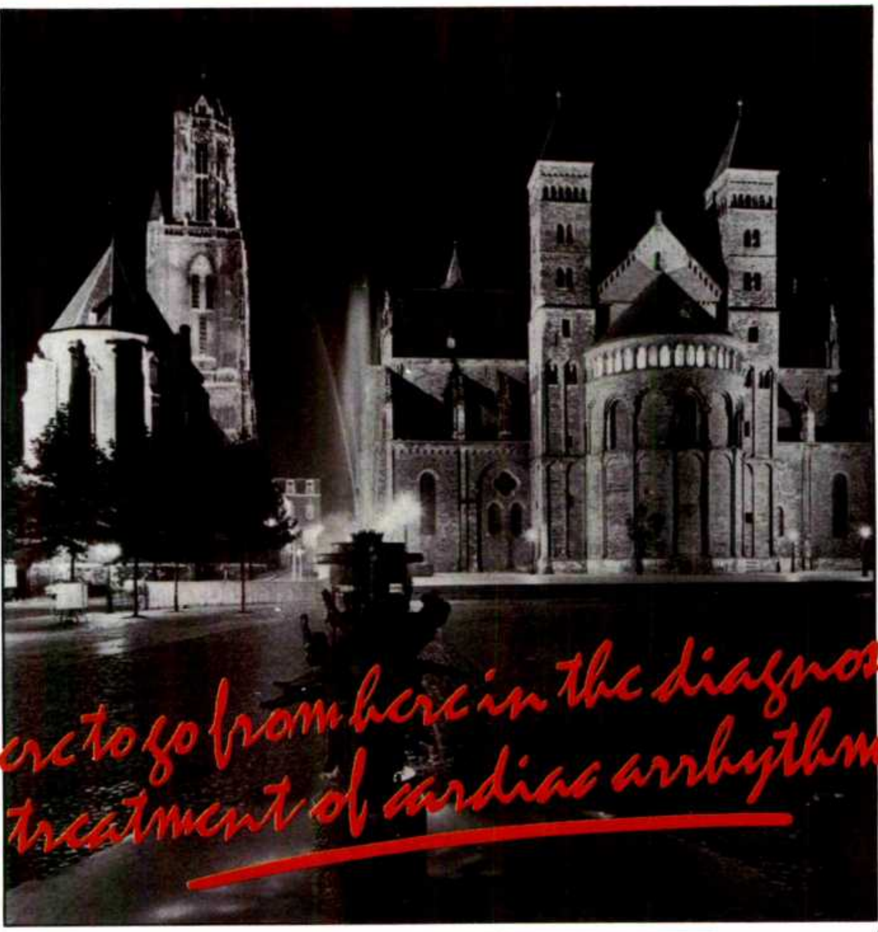

"Where to go from here in the diagnosis and treatment of cardiac arrhythmias"

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Br Heart J 1987;57:279–83

Electrical injury causing ventricular arrhythmias

PETER JØRN JENSEN,*† POUL ERIK BLOCH THOMSEN,*
JENS PETER BAGGER,* AAGE NØRGAARD,* ULRIK BAANDRUP‡

*From the *Department of Cardiology, Aarhus Kommunehospital, Aarhus; the †Department of Internal Medicine, Silkeborg Centralsygehus, Silkeborg; and the ‡Department of Pathology, Aarhus Kommunehospital, Aarhus, Denmark*

SUMMARY Dangerous or long lasting ventricular arrhythmias developed in three patients who had sustained an electrical injury in which current passed through the thorax. In all three cases there was a delay of 8–12 hours between the injury and the onset of symptoms. The ventricular arrhythmias were severe and long lasting. In two of the three patients, ventricular tachycardia or ventricular fibrillation or both occurred and in one patient ventricular parasystole developed. No enzymatic evidence of myocardial necrosis was found but the results of an endomyocardial biopsy carried out in two of the three patients showed focal myocardial fibrosis and increased numbers of Na, K-pumps. The two patients with ventricular tachycardia became symptom free after appropriate antiarrhythmic treatment and in the third patient ventricular parasystole disappeared spontaneously within two years.

Patients sustaining electrical injury in which current passes through the thorax should be monitored electrocardiographically for at least 24 hours, and patients with unexpected arrhythmias should be questioned about previous electrical injury.

A lightning strike is a recognised cause of sudden death. When the mechanism of such death was investigated in 1775 it was found that an electrical shock applied to a head stunned hen whereas another shock to the sternum resuscitated it.[1] In 1850 it was shown in a dog that application of a current to the exposed heart was followed by very rapid and irregular movements of the ventricles—that is, probably ventricular fibrillation.[2]

Nowadays electrical injuries are common. Several factors such as voltage, tissue resistance, tissue susceptibility, type of current, current pathway, site, and duration of electrical contact determine the severity and distribution of the injury.[3] The heart in particular is liable to damage by electrical injury. Thus high voltage (>500 V, direct or alternating current) and lightning can cause sudden death from cardiac arrest, but the low voltage (110–380 V, alternating current 50–60 Hz) used in household electrical equipment can also cause sudden death, usually from ventricular fibrillation.[3 4] Less serious transient electrocardiographic changes have also been described after electrical injury.[5] Furthermore, electrical injury has been diagnosed on the basis of enzyme changes indicating myocardial necrosis.[6 7] Finally, countershock applied for cardioversion can be followed by serious arrhythmias, either immediately or within a few hours,[8 9] or by transient ST segment elevation.[10] The effect of electrical injury on the heart has been demonstrated at necropsy in fatal cases and non-invasively in survivors by electrocardiography, enzyme activity, and echocardiographic examination.[7]

We report three cases of non-fatal electrical injury that were followed by delayed serious ventricular arrhythmias. Endomyocardial biopsy specimens were taken from two of the patients. Microscopy showed myocardial fibrosis.

The membrane bound enzyme, the Na, K-ATPase or Na, K-pump, performs the transport of sodium ions out of the cell and potassium ions into the cell and is essential for the specific properties of muscle and nerve tissue such as contractility and excitability.[11] We estimated the concentration of this pump in the endomyocardial biopsy specimens by measuring binding of [^{3}H] ouabain.[12]

Requests for reprints to Dr Peter Jørn Jensen, Department of Cardiology, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark.

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Patients and methods

ELECTROPHYSIOLOGICAL EXAMINATION

Electrophysiological provocation was performed as described elsewhere.[13] Electrode catheters were introduced percutaneously and positioned high in the right atrium, the His bundle region, and in the right ventricle. Programmed ventricular stimulation was carried out in the right ventricular apex or outlet tract and consisted of pacing with a current of twice diastolic threshold with an impulse duration of 2 ms, and a basic cycle length of 500 ms for eight beats followed by single or double ventricular extrastimuli with varying coupling intervals. If this failed to induce ventricular tachycardia the basic cycle length was reduced to 460 ms and eventually to 400 ms. Finally, if this stimulation procedure failed to induce ventricular tachycardia we used burst pacing with bursts of eight beats with a cycle length of from 300 ms to 200 ms.

ENDOMYOCARDIAL BIOPSY SAMPLING

The left heart was catheterised from the femoral approach. After coronary angiography five endomyocardial biopsy specimens were taken from the left ventricle with Cordis biopsy forceps. Three of the biopsy samples were taken for microscopy and two were frozen (−20°C) for assay of the Na, K-pump.

ASSAY OF THE NA, K-PUMP

Binding of [^{3}H] ouabain was measured as described elsewhere.[12] The biopsy specimens were incubated twice in a TRIS sucrose buffer containing 10 mmol/l TRIS chloride, 3 mmol/l magnesium sulphate, 250 mmol/l sucrose, 1 mmol/l vanadate, and 1×10^{-6} mol/l [^{3}H] ouabain at 37°C for 60 min each. This was followed by four washes at 0°C for another 30 minutes each to remove [^{3}H] ouabain which was not bound to its receptor. After blotting, the samples were weighed and 5% trichloroacetic acid was added. After overnight extraction and liquid scintillation counting, the amount of [^{3}H] ouabain bound to the biopsy specimens was calculated on the basis of the specific activity of the incubation medium. After correction for non-specific uptake determined in the presence of surplus of unlabelled ouabain, results were expressed as pmol of [^{3}H] ouabain per g wet weight of muscle tissue.

Results

PATIENT 1

A 43 year old previously healthy male electrician sustained an electrical injury (3000 V, direct current) from one hand to the other. Twelve hours later while he was playing football he fainted suddenly with cardiac arrest. Resuscitation was started immediately. When he arrived at the local hospital ventricu-

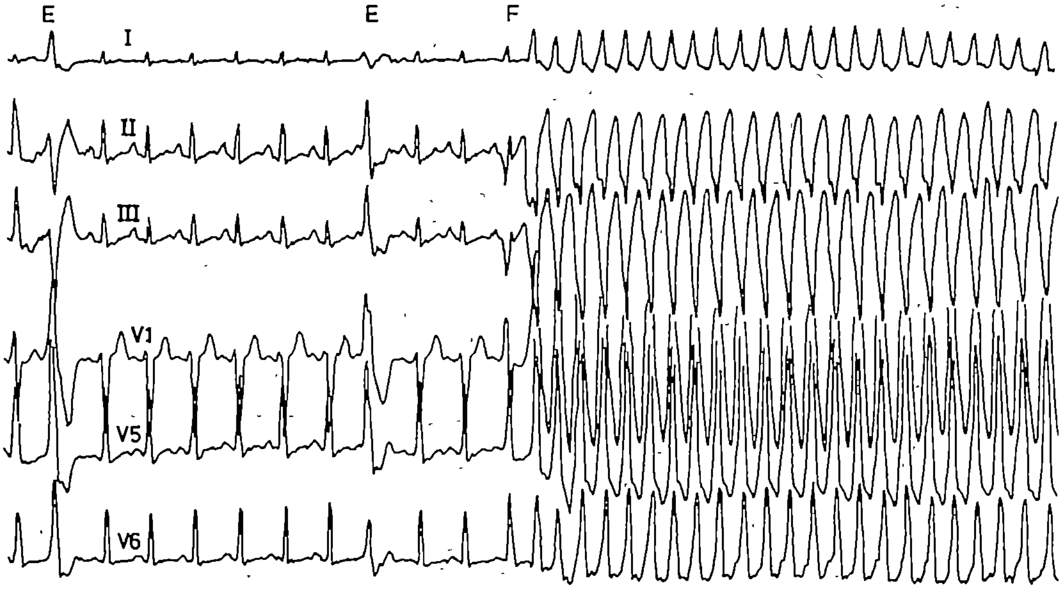

Fig 1 *Electrocardiogram showing the onset of ventricular tachycardia with a frequency of 210 beats per minute just after exercise test in patient 1. The QRS configuration shows right bundle branch block suggesting a left ventricular focus. There were two ventricular extrasystoles (E) of different QRS configuration immediately before ventricular tachycardia started with a fusion beat (F) (paper speed 25 mm/s).*

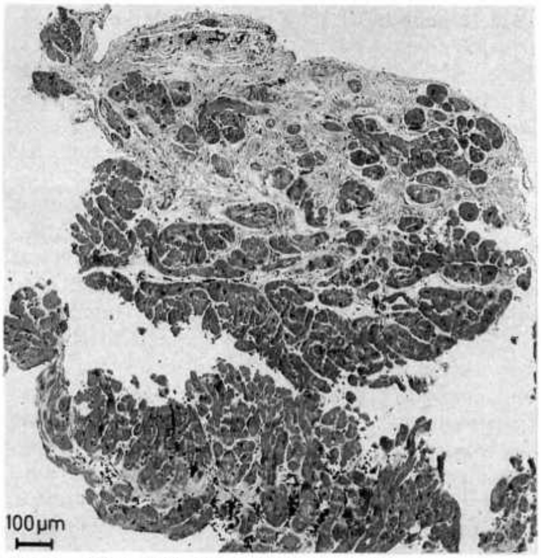

Fig 2 *Left ventricular endomyocardial biopsy specimen from patient 1 showing endocardial and subendocardial fibrosis. Single myocytes are encased by the dense collagen tissue (elastic Van Gieson).*

lar fibrillation was present and he was successfully treated with a direct current countershock. Electrocardiograms recorded half an hour later and in the next few days were normal. Furthermore, activities of coronary enzymes, including creatine kinase B, and serum potassium were normal. A new attack of ventricular fibrillation occurred six days after the accident while he was not being monitored. Conversion to sinus rhythm by direct current countershock was successful.

Six months later he fainted suddenly while bicycling; again there was a cardiac arrest. He was resuscitated. On his admission to the local hospital the electrocardiogram showed ventricular fibrillation and the rhythm was again converted by a direct current countershock. The resting electrocardiogram, echocardiographic examination, and coronary arteriography were normal. Exercise testing showed a working capacity of 300 W for 18 minutes before general exhaustion. Just after the test, however, ventricular tachycardia developed (fig 1). This lasted for 54 s with a frequency of 210 beats per minute (cycle length 290 ms). The QRS configuration during this tachycardia showed right bundle branch block consistent with a left ventricular focus. An identical ventricular tachycardia could be induced by burst pacing at a cycle length of 230 ms in the right ventricular outlet tract. The induced ventricular tachycardia degenerated within a minute to ventricular flutter and fibrillation and the patient was given a direct current countershock. Left ventricular endomyocardial biopsy specimens showed focal myocardial fibrosis (fig 2) and a Na, K-pump concentration of 600 pmol/g wet weight. After administration of sotalol 80 mg three times a day exercise testing was normal and it was no longer possible to induce ventricular tachycardia by electrophysiological provocation.

PATIENT 2

A 45 year old previously healthy woman sustained an electrical injury in which current (380 V, 50 Hz)

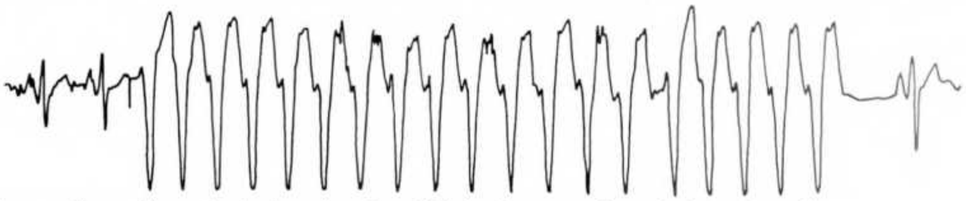

Fig 3 *Electrocardiographic monitoring in patient 2 on CM showing a run of ventricular tachycardia with a frequency of 170 beats per minute lasting 7·4 seconds (paper speed 25 mm/s).*

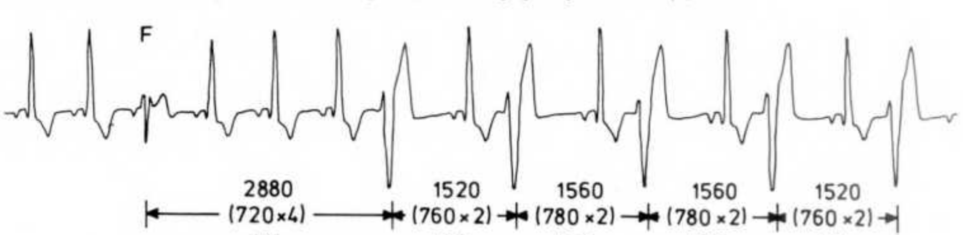

Fig 4 *Electrocardiographic monitoring in patient 3 on CM showing ventricular parasystole with fusion beat (F), variable coupling interval, and a minimum manifest interectopic cycle length of 760 (720–780) ms (paper speed 25 mm/s).*

passed from one arm to the other. Eight hours later she had dizzy spells and palpitation. Despite daily attacks she did not consult her physician until two months later. Ambulatory Holter monitoring showed frequent runs of ventricular tachycardia (170 beats per minute) that lasted up to two minutes. These were associated with dizzy spells (fig 3). At admission to hospital the patient mentioned the previous electrical injury. Resting electrocardiogram, coronary enzyme concentration, and serum potassium concentration were normal. Exercise testing and coronary arteriography were also normal. Left ventricular endomyocardial biopsy specimens showed focal myocardial fibrosis and a Na, K-pump concentration of 463 pmol/g wet weight. She has been treated with mexiletine for six months with excellent effect on the ventricular tachycardia and its symptoms.

PATIENT 3

A 34 year old previously healthy man sustained an electrical injury when current (220 V, 50 Hz) passed from his left hand to his right shoulder. Twelve hours later he experienced chest pain and palpitation. He was admitted to the hospital and physical examination was normal except for a pericardial friction rub. Electrocardiographic monitoring showed ventricular parasystole with highly variable coupling intervals, fusion beats, and a minimum manifest interectopic cycle length of 760 (720–780) msec (fig 4). During the next few days the electrocardiogram showed transient ST segment depression and negative T waves in leads I, II, III, and V4–6. All laboratory tests were normal including creatine kinase B, serum potassium, and virus titres. The exercise electrocardiogram was normal and parasystole disappeared completely when the heart rate exceeded 120 beats per minute. Thallium-201 myocardial exercise testing and cross sectional echocardiography were normal. Coronary arteriography, electrophysiological provocation, and endomyocardial biopsy were not considered to be justified.

Holter monitoring at two weeks and three, six, 12, 24, and 48 months after the injury showed a gradually decreasing number of ventricular parasystolic beats with unchanged minimum manifest interectopic cycle length. Within two years the ventricular parasystole had completely disappeared.

Discussion

In the present study there was a delay between electrical injury and the onset of arrhythmias. Cardiac arrhythmias and conduction disturbances such as ventricular fibrillation, ectopic focal arrhythmia, and bundle branch block have been reported previously in patients who have sustained an electrical injury. These arrhythmias and especially ventricular fibrillation, however, seem to have developed immediately after injury. A delay between injury and onset of arrhythmias does not seem to have been reported before.[3 4 7]

Arrhythmias are often seen after cardioversion by direct current countershock. These can be either immediate or delayed. Thus ventricular fibrillation was seen immediately after cardioversion in 26 of 1046 patients whereas in five patients ventricular fibrillation was delayed from 5 minutes to 6 hours after cardioversion and tended to recur after defibrillation.[9] Unlike our patients, however, these five patients were heavily digitalised and four had hypokalaemia.

Because current tends to course along the neurovascular bundles, the heart is highly susceptible to injury when an electrical current passes through the thorax. Generally, however, in most patients who suffered electrical injury there were no major arrhythmias.[3 4] This may be because evidence about whether the current had passed through the thorax or not was not specifically sought.

Several theories have been advanced to explain the effects of electricity on the heart. The development of patchy necrosis after electrical injury has been suggested.[7] This theory is supported by our findings in the two patients in whom endomyocardial biopsy was performed. To our knowledge abnormal findings in the endomyocardial biopsy specimens of survivors of electrical injury have not been reported before. The biopsy specimens were obtained two and six months after the injury and the patchy fibrosis that we found at this time could explain the development of early arrhythmias. Furthermore, the fibrotic tissue found in the myocardium might be a potential chronic arrhythmogenic focus.

We found Na, K-pump concentrations of 463 and 600 pmol/g wet weight in two endomyocardial biopsy specimens assayed for [^{3}H] ouabain binding capacity. In 15 patients in permanent sinus rhythm the mean (SE) concentration was 413 (26) pmol/g wet weight.[12] Although normal perfusion prevents permanent changes in the extracellular potassium concentration, an increased Na, K-pump concentration may be associated with transient and localised changes in sodium and potassium transport, potassium concentration, and membrane potential. This could be important in the development of arrhythmias.[14]

None of our patients had ischaemic heart disease and there was no electrocardiographic or serological evidence of pericarditis or myocarditis. The pericardial friction rub heard in patient 3 may have been caused by a small pericardial haemorrhage, a feature which has already been found at necropsy in a person who died after being struck by lightning.[5] The histological appearance of the endomyocardial biopsy specimens, however, does not exclude myocarditis.

We believe that patients sustaining an electrical injury in which the current passes through the thorax should be monitored electrocardiographically for at least 24 hours because the onset of arrhythmias may be delayed. Because long lasting and severe arrhythmias can develop under these circumstances, patients with unexpected arrhythmias should be questioned about previous electrical injury.

References

1 Scherf D, Schott A. *Extrasystoles and allied arrhythmias*. 2nd ed. London: William Heinemann Medical Books, 1973:898.

2 Hoffa M; Ludwig C. Einige neue Versuche über Herzbewegung *Zeitschrift fur klinische Medizin* 1850; 9:107–44.

3 Solem L, Fischer RP, Strate RG. The natural history of electrical injury. *J Trauma* 1977;17:487–92.

4 Di Vincenti FC, Moncrief JA, Pruitt BA. Electrical injuries: a review of 65 cases. *J Trauma*. 1969; 9:497–507.

5 Burda CD. Electrocardiographic changes in lightning stroke. *Am Heart J* 1966;72:521–4.

6 Jackson SHD, Parry DJ. Lightning and the heart. *Br Heart J* 1980;43:454–7.

7 Lewin RF, Arditti A, Sclarovsky S. Non-invasive evaluation of electrical cardiac injury. *Br Heart J* 1983;49:190–2.

8 Lown B, Neuman J, Amarasingham R, Berkovits BV. Comparison of alternating current with direct current electroshock across the closed chest. *Am J Cardiol* 1962;10:223–33.

9 Faivre G, Cherrier F, Polu JM. Traitement de la fibrillation auriculaire par choc électrique externe. IV. Complications. *Coeur Med Interne* 1969;8: 487–94.

10 Chun PKC, Davia JE, Donohue DJ. ST-segment elevation with elective DC cardioversion. *Circulation* 1981;63:220–4.

11 Skou JC. Enzymatic basis for active transport of Na^+ and K^+ across cell membrane. *Physiol Rev* 1965;45:596–617.

12 Nørgaard A, Kjeldsen K, Hansen O, Clausen T, Larsen CG, Larsen FG. Quantification of the ^{3}H-ouabain binding site concentration in human myocardium: a post mortem study. *Cardiovasc Res* 1986;20:428–35.

13 Thomsen PEB, Nielsen TT, Albrechtsen O, Mortensen PT, Hansen OKH. Ventricular tachycardia. Electrophysiological principles, medical and surgical treatment. *Ugeskr Laeger* 1984;146:3727–32.

14 Opie LH, Nathan D, Lubbe WF. Biochemical aspects of arrhythmogenesis and ventricular fibrillation. *Am J Cardiol* 1979;43:131–48.

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Case reports

Constitutional predisposition to vasovagal syncope: an additional risk factor in patients exposed to electrical injuries?

PER HERLEVSEN, PER THORGAARD ANDERSEN

From the Department of Cardiology, Aalborg Hospital, Aalborg, Denmark

SUMMARY An hour after a 220 V electric shock a patient who was susceptible to mild vasovagal symptoms in response to emotional stress had a severe episode of cardiac arrest in response to insertion of a cannula. No myocardial damage or conduction abnormalities were detected by serial 12 lead electrocardiograms.

Patients with a history of vasovagal reactions may be at high risk of developing lethal sinus node or conduction disturbances after electrical injuries. Psychological stresses should be avoided in the management of such patients.

Cardiac arrhythmias and conduction disturbances are among the most serious clinical manifestations of electrical accidents.[1] After low voltage injuries (<350 V) arrhythmias and conduction disturbances have been found in 11–39% of the patients.[2] Naturally it is only in fatal cases of high voltage and lightning injuries that the morbid anatomy has been described.[1 3]

The potential lethal effect of autonomic reactions when there is electrical instability in the heart has been described in patients with ischaemic heart disease and in animal experiments.[4 5] We report a patient who fainted soon after a 220 V electric shock. About an hour later sinus arrest developed seconds after the insertion of an intravenous cannula.

Case report

A 33 year old electrician was admitted to hospital after a 220 V AC electric shock. When the shock occurred he was fully conscious and locked on to the wires because of the tetanising effect of the alternating current; he was pulled away by his colleagues. The current, which had passed up one arm and down the other, had caused electrothermal burns on both hands. About 30 seconds after the accident the patient lost consciousness for 10–15 seconds. The pulse was not registered during this event. He regained consciousness spontaneously. At admission to hospital his pulse rate was 80–88 beats/minute, blood pressure was 150/90 mm Hg, and a 12 lead electrocardiogram showed no signs of myocardial injury. A stable sinus rhythm and normal PQ, QRS, and QT intervals were found. The patient's electrocardiogram was monitored continuously. Before the insertion of an intravenous cannula he stated that he was always upset by the sight of blood. He reported fainting after an intramuscular injection and he said that on several occasions he had turned pale and felt dizzy and nauseated at the sight of blood or cannulas. On this occasion as the cannula penetrated his skin (about an hour after the electric shock), sinus bradycardia developed and this led to sinus arrest within 5–10 seconds. The patient lost consciousness, his pupils dilated, and he stopped breathing. Asystole lasted 33 seconds and was interrupted by a

Requests for reprints to Dr Per Herlevsen, Purkervej 7, DK 9520 Skørping, Denmark.

ventricular escape at 17 seconds and a nodal escape at 29 seconds. After 33 seconds a spontaneous sinus impulse was seen but another sinus arrest followed. Electrical cardiac activity then was restored by a blow to the chest and external cardiac compression. During the next three days no arrhythmias or cardiac conduction disturbances were recorded and serial electrocardiograms did not disclose structural damage to the heart. Carotid sinus stimulation was performed two days after the accident and did not provoke bradycardia or conduction disturbances. The patient left hospital in an excellent physical condition after an observation period of three days.

Discussion

Many reports have indicated a relation between psychological stress and sudden death. Engel reviewed 275 patients who died suddenly; 21% died immediately after hearing of the collapse or death of a close relative and another 9% died when such a loss appeared to be a possibility.[6] Twenty per cent died during the first three weeks of acute grief and 3% during mourning or upon anniversary of a death. A similar link between emotional state and sudden death from coronary artery disease was found in another study.[7]

Cardiac arrest after vasovagal reactions to emotional stimuli in otherwise healthy individuals have only rarely been described.[8 9] It is known, however, that strong vagal stimulation in healthy people may induce sinus arrest for 4 to 10 seconds.[10] This prompts the question "Was the sinus arrest caused exclusively by a strong vasovagal reaction or was the cardiac dysfunction induced by the electric shock a contributing factor?"

Neither the history nor the patient's subsequent progress suggested that he had ischaemic heart disease; and contemporary and serial electrocardiograms showed no evidence of structural damage to the myocardium by the electric shock. Minor electrophysiological disturbances in intracardiac electrical conduction and the impulse generating system, however, may not induce recognisable abnormalities in a standard electrocardiogram. Furthermore, the pathophysiological basis of arrhythmias that occur after low voltage electrical accidents without myocardial damage is unknown. Finally, the patient had never before shown such severe vasovagal reaction in response to the insertion of a cannula, though he reported milder vasovagal responses to similar stimuli. For these reasons we believe that the electric shock had enhanced the patient's reaction to such stimuli and to such an extent that was potentially lethal.

Patients with a history of vasovagal reactions may be at increased risk of the development of lethal cardiac conduction disturbances after electrical injuries. It seems reasonable to advise medical and nursing staff to avoid interventions that cause psychological stress in such patients.

References

1 Dixon GF The evaluation and management of electrical injuries. *Crit Care Med* 1983,11.384–7.

2 Egstrup K, Møller M. Is cardiac monitoring necessary after electrical accidents. [English abstract.] *Ugeskr Laeger* 1983;145:2138–9.

3 Hanson CG, McIlwraith GR. Lightning injury. two case histories and a review of management. *Br Med J* 1973;4·271–4.

4 Myers A, Dewar HA. Circumstances attending 100 sudden deaths from coronary artery disease with coroner's necropsies. *Br Heart J* 1975;37:1133–43

5 Skinner JE, Lie JT, Entman ML. Modification of ventricular fibrillation latency following coronary artery occlusion in the conscious pig. The effect of psychologic stress and beta-adrenergic blockade *Circulation* 1975;51:656–67.

6 Engel GL. Emotional stress and sudden death. *Psychol Today* 1977;11:114–8.

7 Bruhn JG, Paredes A, Adsett AC, Wolf S Psychological predictors of sudden death in myocardial infarction. *J Psychosom Res* 1974;18:187–91.

8 Tizes R. Cardiac arrest following routine venipuncture. *JAMA* 1976;236:1846–7.

9 Schlesinger Z, Barzilay J, Stryjer D, Almog CH Life-threatening "vagal reaction" to emotional stimuli. *Isr J Med Sci* 1977;13:59–61.

10 Guyton AC. Control of heart rhythmicity and conduction by the autonomic nerves. In: *Medical physiology*. 6th ed. Philadelphia: WB Saunders, 1981:170–2.

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Extraluminal compression of an aortic graft simulating recoarctation

AUDREY STERN, BRUCE P MINDICH,* JONATHAN L HALPERIN

From the Cardiothoracic Center, Mount Sinai Medical Center, New York, NY, USA

SUMMARY Restenosis rarely develops after surgical correction of coarctation of the aorta in adults. Late morbidity is usually related to residual hypertension or progressive aortic valve disease. A patient in whom symptoms and signs of recurrent coarctation developed 19 years after initial graft repair is described. Dehiscence of the original silk suture line was found at operation. Extensive thrombus had produced graft compression. Milder hypertension persisted in the postoperative period despite relief of the aortic obstruction.

Late morbidity after repair of coarctation of the aorta in adulthood is usually caused by residual hypertension, development of coronary atherosclerosis, aneurysm formation, stroke, aortic valve disease, or congestive heart failure.[1-3] Recoarctation rarely develops when the initial operation is performed in adulthood, but stenosis may develop when the enlarging aorta outgrows a synthetic graft inserted earlier in life. We encountered a case in which apparent recoarctation developed as a result of dehiscence of the original suture line 19 years after initial repair. Extensive thrombus formation resulted in graft compression.

Case report

A 38 year old white woman presented with hypertension and claudication in the legs 19 years after surgery for repair of coarctation of the aorta. She had presented initially with similar findings, and angiography had identified a juxtaductal aortic coarctation beyond the left subclavian artery with preserved distal flow and associated ductus arteriosus. During the original operation the ductus arteriosus was ligated, a long coarctation was resected, and a 14 mm Dacron graft was inserted with a silk suture. The patient did well in the postoperative period; blood pressure became normal, claudication remitted, and she enjoyed an active lifestyle and completed two full term pregnancies without difficulty. At 38 she experienced fatigue and dyspnoea and claudication of the calves, thighs, hips, and buttocks on both sides. She was admitted to hospital with congestive heart failure and the blood pressure was then 230/112 mm Hg. Congestion and hypertension responded to administration of diuretic and vasodilator medications. At readmission her medications included metolazone (10 mg daily) and clonidine (0 1 mg three times a day); she had stopped using aspirin nine months before.

Physical examination found the patient in no distress at rest and well developed with a full, but not webbed, neck. The supine blood pressure was 168/90 mm Hg in the left arm and 180/95 in the right. The heart rate was 60 beats/min with occasional extrasystoles. The lung fields were clear. A systolic murmur was heard over the left chest posteriorly and radiated toward the midline and left renal fossa. Anteriorly, the murmur was heard over the left pectoral and manubrial areas. There was no jugular venous distension and the carotid arterial pulse was normal. An apical mid-systolic murmur and click were heard but no diastolic murmurs were heard. Examination of the abdomen showed no organ enlargement. The femoral pulse and more distal pulses of the legs were delayed and markedly diminished in volume. Systolic pressure at the ankles, registered with the Doppler ultrasound device, was

Present address: *St Luke's-Roosevelt Medical Center, Department of Cardiothoracic Surgery, Amsterdam Avenue and 114th Street, New York, New York 10025

Requests for reprints to Dr Jonathan L Halperin, Division of Cardiology, Mount Sinai Medical Center, Fifth Avenue at 100th Street, New York, NY 10029, USA.

75 mm Hg at rest while supine and 70 mm Hg after exercise.

The electrocardiogram displayed normal sinus rhythm and large voltages characteristic of left ventricular hypertrophy. Chest *x* ray showed normal cardiac dimensions and pulmonary vasculature but there was evidence of mild rib notching. Cross sectional echocardiography showed normal chamber dimensions. The aortic valve was not well visualised; however, intracardiac Doppler analysis demonstrated aortic insufficiency.

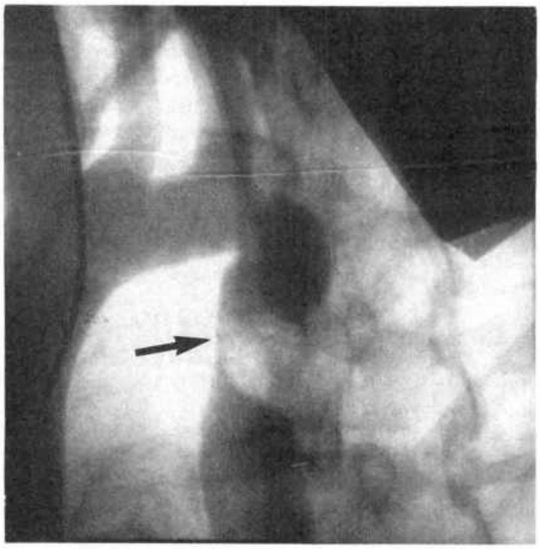

Fig 1 *Aortic angiogram in the left anterior oblique projection showing severe eccentric narrowing beyond the origin of the left subclavian artery as well as a large filling defect at the site of narrowing (arrow).*

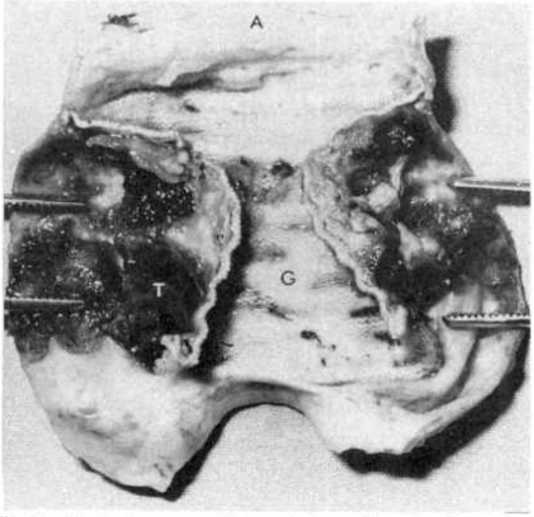

Fig 2 *Excised segment of aorta (A) and graft (G) showing extensive thrombus (T) compressing the lumen of the graft.*

CARDIAC CATHETERISATION AND ANGIOGRAPHY

Right and left heart catheterisation was performed from the right antecubital approach. The pulmonary artery pressure was 30/14 mm Hg and the left ventricular pressure was 240/16 mm Hg at rest. The cardiac index measured by the thermodilution technique was 3 l/min/m^2. Angiography showed severe eccentric narrowing of the descending aorta just distal to the origin of the left subclavian artery and a large filling defect at the site of narrowing (fig 1). Three aortic sinuses were identified and aortic insufficiency (grade 2+) was demonstrated.

SURGICAL FINDINGS AND POSTOPERATIVE COURSE

Left thoracotomy was performed through the original incision site at the level of the previously resected fifth rib. The area of original coarctation repair was identified and appeared well healed without evidence of infection. An aneurysmal dilatation approximately 3·5 cm in diameter was found in the region of the proximal anastomosis. The proximal suture line appeared to have dehisced along half its circumference. Dissection around the graft and extensive thrombus formation had compressed the graft to less than 10% of its potential diameter (fig 2). The distal suture line was intact and there was slight neointimal hyperplasia. The graft was excised and replaced with a new 18 mm preclotted woven Dacron prosthesis and a Prolene suture was used to fashion the end to end anastomosis. Postoperatively, hypertension developed and treatment with intravenous nitroprusside, propranolol, and methyldopa was needed. Eventually an oral regimen of labetalol and diuretic was sufficient to maintain pressure in the normal range and the patient was discharged from the hospital on the eighth postoperative day after an otherwise uneventful recovery. A month after operation she was symptom free, with no dyspnoea or claudication. Blood pressure was well controlled, no murmurs were heard over the thorax, and pulses throughout the legs were strong.

Discussion

Repair of aortic coarctation by synthetic graft replacement has become increasingly common since its introduction in 1960, and the technique was used in approximately 65% of patients in a series reported by DeBakey's group.[1] Features of coarctation calling for graft interposition include *(a)* involvement of a long aortic segment in the coarctation, *(b)* a small calibre proximal aortic segment, *(c)* the need for resection of an associated aneurysm, *(d)* inelasticity of the aorta in older patients, and *(e)* technical intraoperative complications. In all forms of surgery for relief of coarctation, late morbidity and mortality are usually associated with residual hypertension and take the form of myocardial infarction, congestive heart failure, stroke, and aneurysm formation. Important aortic valve disease may also develop but complications directly related to the graft anastomotic suture line are unusual.

Pennington *et al* reported an experience of the Massachusetts General Hospital with surgical treatment of aortic coarctation (1947–76).[4] Fifty nine (36%) of 164 patients underwent resection and interposition grafting. Fifty three per cent of patients aged > 10 years and 66% of patients aged > 40 years had interposition grafts. Only one of the late deaths was related to rupture of a pseudoaneurysm at a silk suture line. This was found 17 years after operation. There were no cases of restenosis in patients with synthetic grafts or even of relative stenosis caused by outgrowing the graft.

Of the 190 patients who underwent surgical correction of coarctation of the descending aorta at Baylor, late postoperative mortality occurred in 18 cases.[1] Two thirds of these deaths were attributed to myocardial infarction or heart failure. Fatal rupture of aortic aneurysm occurred in two cases. Late morbidity developed in 14 patients: recurrent coarctation in three, true aneurysm in four, and pseudoaneurysm in one; six patients required aortic valve replacement. Aneurysms generally developed in patients with longstanding hypertension. The data provided mean that we cannot tell which patients were treated with synthetic grafts and which by primary anastomosis, but the rather low rate of recurrent stenosis was ascribed to the high proportion of cases managed with grafts.

Although resection and primary end to end anastomosis is the procedure of choice for repair of coarctation of the aorta, many patients, especially those undergoing late repair, require interposition of a synthetic graft. After reports of suture line failures with pseudoaneurysm formation[5] silk has been abandoned as a suture material for graft anastomosis. In patients presenting with signs and symptoms of recoarctation long after initial repair by interposition of a synthetic graft, the differential diagnosis includes coarctation at a second site, stenosis within the graft, or functional stenosis related to further growth of the aorta. Though less common, the possibility of a significant anastomotic complication, such as occurred in our patient, warrants prompt evaluation if catastrophic rupture is to be avoided.

References

1 Lawrie GM, DeBakey ME, Morris GC, Crawford ES, Wagner WF, Glaeser DH. Late repair of coarctation of the descending thoracic aorta in 190 patients. *Arch Surg* 1981;**116**:1557–60.

2 Liberthson RR, Pennington DG, Jacob ML, Daggett WM. Coarctation of the aorta: review of 234 patients and clarification of management issues. *Am J Cardiol* 1979;**43**:835–9.

3 Schuster SR, Gross RE. Surgery for coarctation of the aorta: review of 500 cases. *J Thorac Cardiovasc Surg* 1962;**43**:54–70.

4 Pennington DG, Liberthson RR, Jacobs M, Scully H, Goldblatt A, Daggett WM. Clinical review of experience with surgical repair of coarctation of the aorta. *J Thorac Cardiovasc Surg* 1979;77:217–29.

5 Shaw RS. Reconstructive vascular surgery. *N Engl J Med* 1962;**266**:339–46.

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A ruptured large aneurysm of the ductus arteriosus

SHOJI TSUJIMOTO, KUNIHIKO HIROSE, AKIRA OHYAGI

From the Cardiovascular Department, Ohtsu Red-Cross Hospital, Nagara, Ohtsu City, Japan

SUMMARY A 60 year old man was admitted with acute back pain followed by hoarseness. An aneurysm of the ductus arteriosus Botalli was diagnosed and an operation was recommended because of the high risk of complications such as rupture, embolism, or infection. The patient and his family refused surgery, however. The patient died suddenly of a rupture of the aneurysm a year later; necropsy confirmed the diagnosis. Several diagnostic methods were used and enhanced computed tomography gave the best representation of the aneurysm as it was seen at necropsy. This case indicates that enhanced computed tomography is probably the most useful investigation in patients with this type of aneurysm and it confirms the importance of an aneurysmectomy.

An aneurysm of the ductus arteriosus Botalli is an uncommon cardiovascular anomaly. Cases in adults are rare; only 22 had been reported by 1984.[1 2] We report a case of an aneurysm of a non-patent ductus arteriosus in an adult. In this case the diagnosis was made clinically but surgery was refused and death occurred suddenly about one year after diagnosis. Necropsy showed a left haemothorax caused by a ruptured aneurysm of a non-patent ductus arteriosus. This case raises several important issues—such as the most useful diagnostic methods and the importance of surgery.

Case report

A 60 year old man was admitted with acute severe back pain followed by hoarseness in January 1983. Five days before admission he had had acute back pain lasting all day. He visited the otolaryngological department of our hospital because of hoarseness, and left recurrent nerve paralysis was diagnosed. He was referred to the cardiovascular department because of an abnormally large aortic shadow on the chest *x* ray. He had a 10 year history of diabetes mellitus and hypertension, which were well controlled. There was no history of chest trauma.

At admission blood pressure was 142/90 mm Hg and a grade 3/6 mid-systolic murmur was audible at the pulmonary area (the second intercostal space along the left sternal border). A chest *x* ray showed a smooth rounded dense area in the left hilar region that was contiguous with the aorta, reduced lung markings throughout the left lung, and a cardiothoracic ratio of 0·54. The electrocardiogram disclosed right ventricular hypertrophy (fig 1). A serological test for syphilis was negative. An enhanced computed tomogram of the chest showed a large aneurysm between the ascending aorta and the descending aorta that contained a mural thrombus (fig 2). The maximum transverse diameter of the aneurysm was 118 mm. A pulmonary scintigram showed absence of left lung perfusion. Right heart catheterisation showed mild elevation of right ventricular pressure (51 mm Hg systolic/6 mm Hg end diastolic) and a systolic pressure gradient of 25 mm Hg between the main (52/6 mm Hg) and right pulmonary arteries (27/8 mm Hg). This systolic pressure gradient was thought to be the cause of the heart murmur in this patient. Pulmonary arteriography showed that the left pulmonary artery was completely obstructed at its origin. The laevophase of the same arteriogram showed a large aortic aneurysm protruding from the inferior border of the aortic arch.

Because of the high risk of fatal complications such as rupture, embolism, and infection, operation was recommended, but the patient and his family refused it and he was discharged. He was treated medically to reduce afterload. On 13 December 1983 the patient again presented with severe chest pain, which lasted until he died early the next morning.

Necropsy showed approximately 2 litres of bloody

Requests for reprints to Dr Akira Ohyagi, Cardiovascular Department, Kyoto Katsura Hospital, 17 Hirao-Cho Yamada Nishikyo-Ku, Kyoto City, Zip 615 Japan.

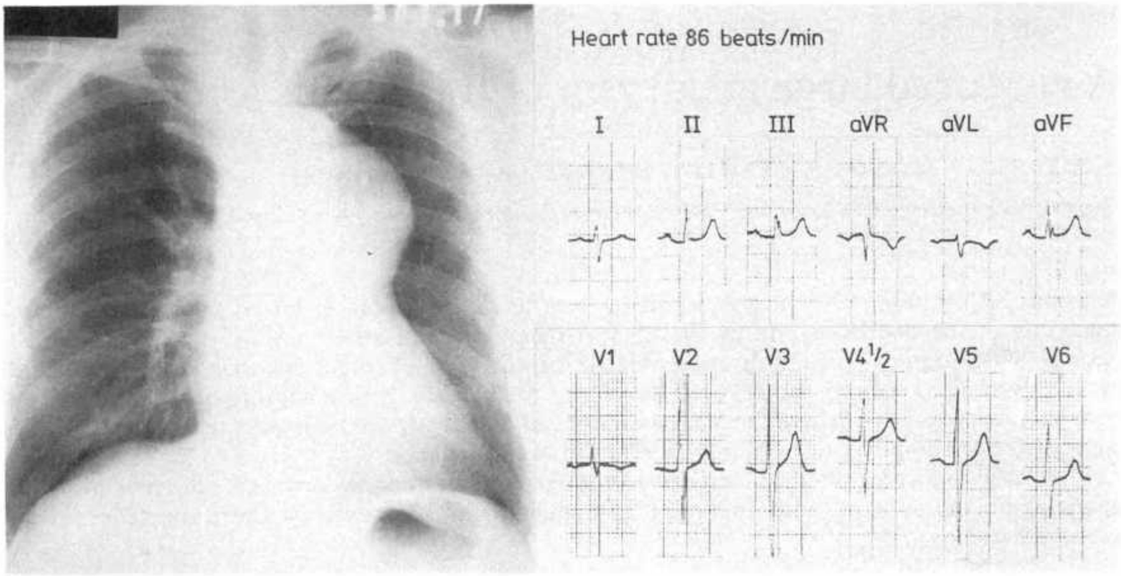

Fig 1 *Chest radiogram (left) and electrocardiogram (right) on admission. There is a smooth rounded dense area in the left hilar region contiguous with the aorta and reduced lung markings throughout the left lung. The electrocardiogram disclosed right ventricular hypertrophy.*

pleural fluid in the left pleural cavity and a ruptured large thoracic aneurysm surrounded by the aortic arch. The aortic ostium of the aneurysm was patent and was located at the site of the ductus arteriosus Botalli. The pulmonary end of the aneurysm was closed. This ligamentum arteriosus was not identified because of severe adhesions between the main pulmonary artery and the aneurysm. Most of its cavity was occluded by a mural thrombus and only the central part of the aneurysm was patent. The aneurysm protruded anteriorly and to the left. There was a rupture 5 cm long on the anteroinferior wall of the aneurysm. The aneurysm completely compressed the left pulmonary artery and moderately compressed the right pulmonary artery. The right ventricle showed concentric hypertrophy; its wall was 4 mm thick. There was severe atherosclerosis with calcification in the aorta.

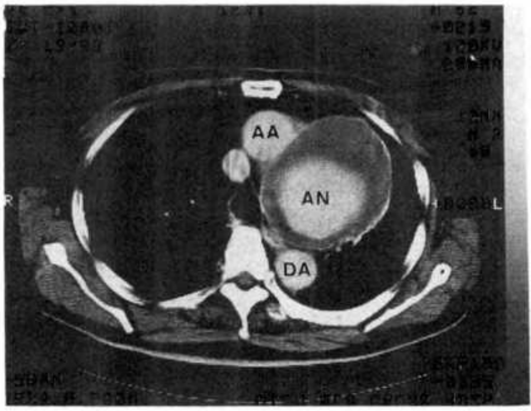

Fig 2 *Enhanced computed tomogram of the chest. A large aneurysm is located between the ascending aorta and the descending aorta. Most of the aneurysmal cavity is occupied by a mural thrombus. AA, ascending aorta; DA, descending aorta; AN, aneurysm.*

Discussion

Aneurysms originating from the ductus arteriosus Botalli are called ductal aneurysms. When the aortic ostium of the duct fails to close the systemic blood pressure in the aorta may lead to aneurysmal dilatation of the duct.[2-4]

Aneurysm of the ductus arteriosus Botalli was first described by Martin *et al* in 1827[6]; only 22 adult cases had been reported by 1984. Although "the prognosis in the majority of infantile ductus arteriosus aneurysms without treatment is good",[5] in adults rupture, embolism, or infection are common fatal complications. Mitchell *et al* noted that 60% of reported patients died of complications related to the aneurysm.[1] Operation is recommended for aneurysms that are > 3 cm in diameter, if symptoms indicate that an adjacent organ has been affected by the aneurysm, or if there is progressive enlargement of the aneurysm.[1 3 5] In our case we advised operation but unfortunately the patient and his family refused. The patient died a year after diagnosis of the aneurysm.

This case indicates that operation may be mandatory. A correct diagnosis is essential especially before operation. In our patient enhanced computed tomography gave the most reliable information and was as useful as invasive examinations such as angiocardiography. Until now angiocardiography has been considered to be one of the most reliable tools for the diagnosis of aneurysms, although there is a risk of rupturing the aneurysm when contrast medium is injected into the aorta under high pressure. We recommend enhanced computed tomography as a very useful tool for diagnosis of aneurysm of the ductus arteriosus. It should lead to "the correct preoperative diagnosis and the proper surgical management".[4]

We thank Dr Alice S Cary, and Dr Yasuyuki Nakamura for their help in the preparation of this paper.

References

1. Mitchell RS, Seifert FC, Miller DC, Jamieson SW, Shumway NE. Aneurysm of the diverticulum of the ductus arteriosus in the adult. *J Thorac Cardiovasc Surg* 1983;**86**:400–8.
2. Danza FM, Fusco A, Breda M, Bock E, Lemmo G, Colavita N. Ductus arteriosus aneurysm in an adult. *Am J Roentgenol* 1984;**143**:131–3.
3. Falcone MW, Perloff JK, Roberts WC. Aneurysm of the nonpatent ductus arteriosus. *Am J Cardiol* 1972;**29**:422–6.
4. Cohen BA, Efremidis SC, Dan SJ, Robinson B, Rabinowitz JG. Aneurysm of the ductus arteriosus in an adult. *J Comput Assist Tomogr* 1981;**5**:421–3.
5. Heikkinen ES, Simila S, Laitinen J, Larmi T. Infantile aneurysm of the ductus arteriosus. *Acta Paediatr Scand* 1974;**63**:241–8.
6. Martin. Dilatation anéurysmal du canal arteriel. *Bull Soc Anat Paris* 1827;**22**:17.

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Entanglement of embolised thrombus with an endocardial lead causing pacemaker malfunction and subsequent pulmonary embolism

R A PERRY, D B CLARKE, M F SHIU*

*From the Departments of Cardiovascular Medicine and *Cardiothoracic Surgery, Queen Elizabeth Hospital, Edgbaston, Birmingham*

SUMMARY A 67 year old woman with a permanent pacemaker was admitted with pulmonary oedema and mitral valve incompetence two months after a myocardial infarction. Echocardiograms showed good left ventricular function and a large coil of apparent thrombus in the right atrium prolapsing into the right ventricle. Intermittent loss of pacemaker sensing and capture was noticed on admission and probably caused the supraventricular tachycardia and ventricular fibrillation that occurred before an exploratory bypass operation. At operation rupture of the papillary muscle was found and the mitral valve was replaced. A large piece of thrombus was retrieved from the right pulmonary artery. The right heart contained no clot and the pacemaker wire was not displaced.

It is envisaged that the strand of venous thrombus was caught in the permanent pacing wire at the tricuspid valve level resulting in an unusual case of pacemaker malfunction. The eventual poor outcome was almost certainly influenced by the arrhythmias and pulmonary embolism caused by the clot and might have been avoided by early operation.

Thromboembolism associated with endocardial pacing leads has been described in many forms.[1–3] The thrombi usually form in situ, especially around the entry site; they propagate centrally and result in venous obstruction and pulmonary embolism. Serious haemodynamic disturbances, sometimes leading to sudden death, have been described.[4] We report here a patient with a deep vein thrombus that became entangled with an endocardial pacemaker lead and caused pacemaker failure.

Case report

A 67 year old woman was admitted with increasing shortness of breath and orthopnoea. A permanent pacemaker had been inserted nine months earlier for complete heart block that was discovered before a hysterectomy operation. The pacemaker was a ventricular demand system which could not be programmed. Two months before the present admission she was treated in another hospital for an inferior myocardial infarction. This was complicated by congestive cardiac failure and mitral regurgitation. Initially, her heart failure had been controlled by daily doses of digoxin 0 0625 mg, frusemide 80 mg, and spironolactone 100 mg, with captopril 12·5 mg three times a day. On examination at this admission she was dyspnoeic at rest. The heart rate was 80 beats/min and irregular. The blood pressure was 110/70 mm Hg and the jugular venous pressure was elevated by 5 cm. There was an apical systolic murmur radiating to the axilla and bilateral basal rales in the chest. At admission the electrocardiogram showed sinus rhythm with atrial and ventricular extrasystoles. Inappropriate pacing artefacts caused by undersensing of the pacemaker system occurred when the patient lay on her right side. There was also evidence of intermittent exit block.

Chest *x* ray showed cardiomegaly, pulmonary congestion, and the pacing wire in the normal position. She was treated with bed rest and the dose of diuretics was increased. A diagnosis of recent myocardial infarction was excluded and plans were made to investigate her with a view to mitral valve replacement. Pacemaker malfunction was unexplained.

Cross sectional echocardiography showed good left ventricular function. Coincidentally, a sus-

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Requests for reprints to Dr R A Perry, University Department of Cardiovascular Medicine, The Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Edgbaston, Birmingham B15 2TH.

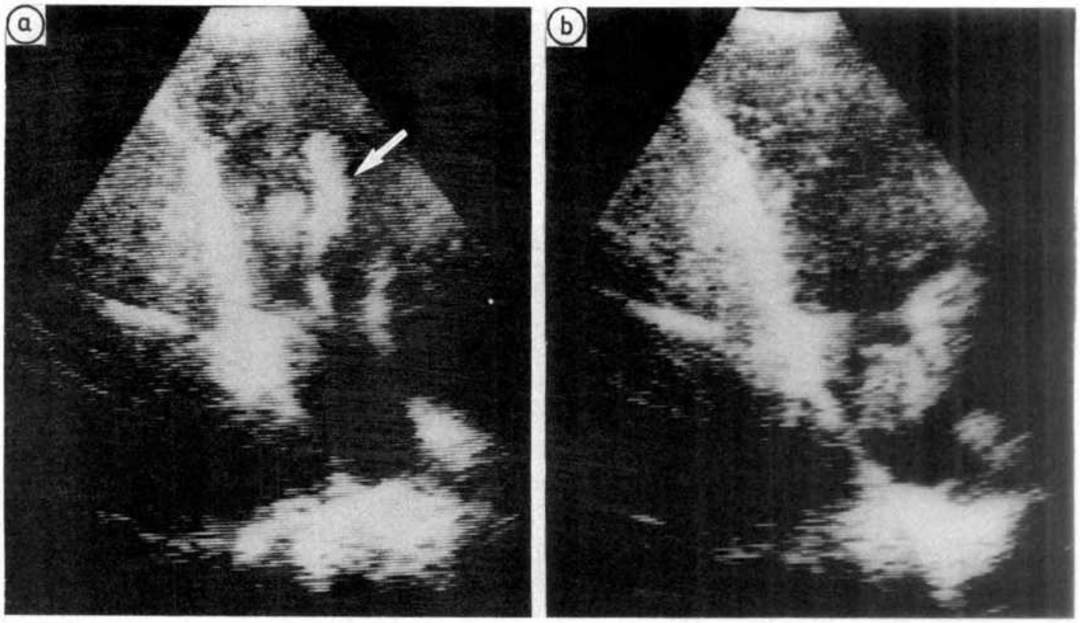

Fig 1 *Apical view of cross sectional echocardiograph showing right ventricle containing thrombus (arrowed) round pacing lead in diastole (a) and empty right ventricle with thrombus in right atrium in systole (b).*

picious mass was seen prolapsing through the tricuspid valve (fig 1). It appeared to be related to the wire, though no points of attachment to the wire or the tricuspid valve could be seen. The features were thought to be consistent with an intracardiac clot or myxoma and right heart catheterisation was avoided. Left heart catheterisation was performed and the left ventricular cineangiogram confirmed severe mitral regurgitation with good overall ventricular function.

A day after admission she had an episode of spontaneous ventricular tachycardia while lying on her right side and the next day ventricular fibrillation developed. This responded to cardiopulmonary resuscitation and DC cardioversion. It was decided that the arrhythmia was due to pacekmaker undersensing. Further episodes were prevented by suppression of the permanent pacemaker with an external pacemaker and skin electrodes. Her general condition deteriorated and the planned mitral valve replacement was brought forward. On the morning of the operation a repeat echocardiogram showed that the right sided echo was normal apart from the presence of an endocardial wire. At operation the right atrium and ventricle were empty and the pacing wire was embedded in the tip of the right ventricle. In view of the echocardiographic findings the pulmonary artery was opened. A 5 cm by 1·5 cm thrombus was removed from the right pulmonary artery. Exploration of the left heart showed papillary muscle rupture; mitral valve replacement was carried out as planned.

The sausage shaped thrombus had a smooth ridge in the mid-portion suggesting that this was the site of entanglement with the pacemaker wire (fig 2). The histological appearance of the thrombus was typical of a venous cast of a clot arising from the deep veins.

After operation progressive renal failure developed. The patient had a stroke and died of bronchopneumonia nine days after operation.

Discussion

There were some salutary lessons to be learned from this case. The predominant cardiac problem was myocardial infarction complicated by papillary muscle rupture causing congestive cardiac failure. Without mitral valve replacement it is unusual for patients with post-infarction rupture of the papillary muscle to survive more than a few days. Some patients have survived for up to three months[5] with complete papillary muscle rupture as was the case with our patient. With partial rupture the outlook is more favourable with up to 40% of patients surviving for more than a month.[6]

The preoperative course in this patient was complicated by supraventricular and ventricular arrhythmias induced by pacemaker malfunction.

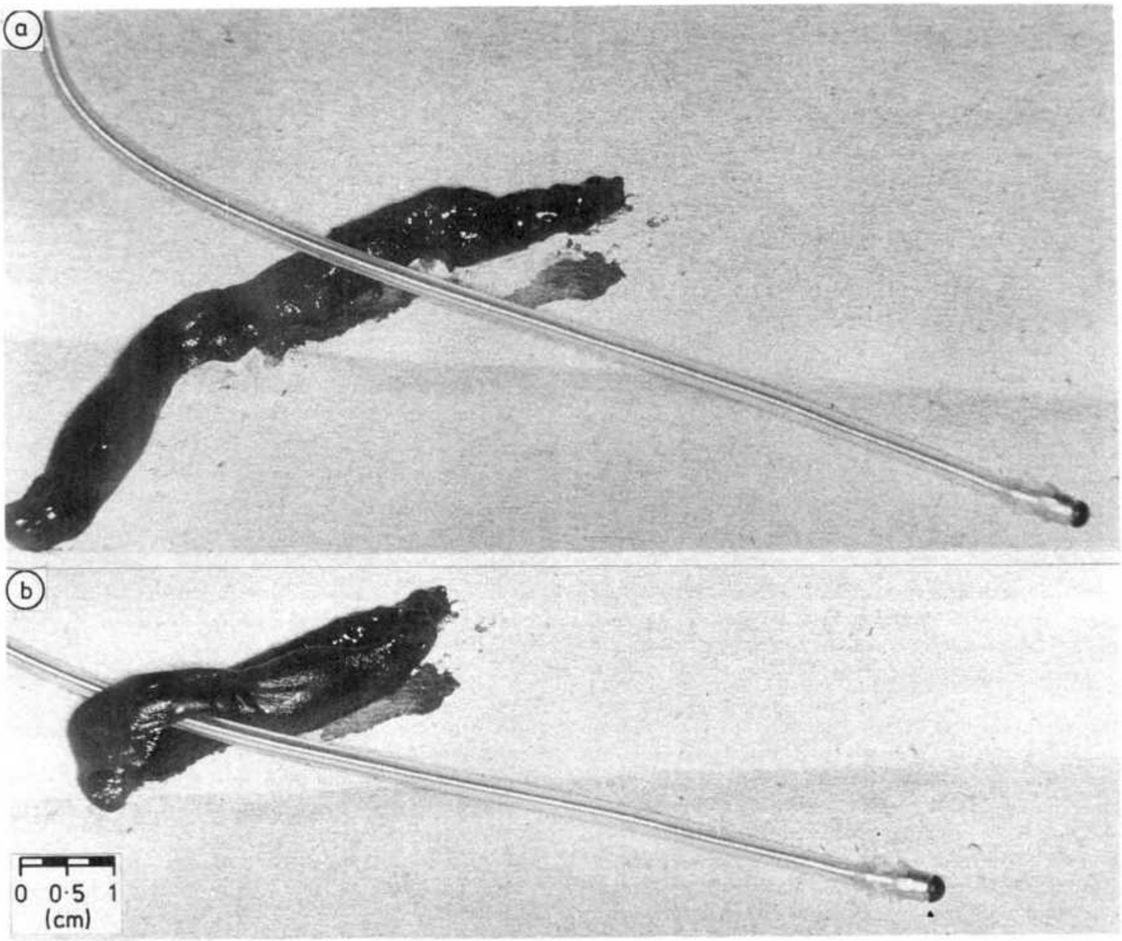

Fig 2 *Thrombus removed from right pulmonary artery showing full length (a) and likely association with pacing wire (b).*

Subsequent electrical testing of the demand pacemaker showed that it was working normally as was the endocardial lead, which was intact and embedded securely in the apex of the right ventricle. On the basis of our echocardiographic observations we believe that the intermittent pacemaker malfunction, which was clearly related to posture, was due to the pacemaker wire being pulled during systole by the prolapse of the entangled mass (fig 2). The pacemaker was suppressed and the patient had no further arrhythmic events before operation. In the postoperative period the pacemaker functioned normally on demand.

The shape and histology of the thrombus suggest that its source was the deep veins. There have been several reports of the detection by echocardiography of entrapment of thrombi in the right atrium and the tricuspid apparatus.[7-10] Attempts may be made to remove the thrombus surgically or to allow the thrombus to resolve after treating the patients with anticoagulants. Brown and Anderson have reported reduction in thrombus size and mobility in a patient treated with heparin followed by oral anticoagulants; however, their patient was too frail for operation.[11] Come reports a patient who continued to have pulmonary emboli despite treatment with both streptokinase and subsequent heparin.[12] In a small series Felner *et al* showed that despite anticoagulation half their patients eventually required surgery for repeated pulmonary emboli from right atrial thrombi.[13] In one patient, however, resolution occurred without any treatment. In the same paper a review of published reports suggested that immediate removal of thrombus under cardiopulmonary bypass is the treatment of choice. In none of these cases, however, was the thrombus associated with a pacemaker.

It is difficult to say to what extent the pacemaker thrombus contributed to the patient's death. The clinical state deteriorated sharply after an episode of ventricular fibrillation during which cardiopulmonary massage was performed before successful DC cardioversion. If the thrombus had been removed surgically soon after its detection by echocardiography there would have been no risk of its becoming dislodged into the pulmonary circulation during this period of mechanical asystole and physical disturbance. Even if the ventricular fibrillation had been a direct consequence of clot embolisation, early surgery would also have removed this risk.

To our knowledge this is the first report of a sling of embolising clot around an endocardial pacing lead causing pacemaker malfunction and subsequent pulmonary embolism. Although our patient had a potentially lethal condition and post-infarction mitral incompetence, both these additional factors almost certainly contributed to the outcome. The case confirms the usefulness of cross sectional echocardiography in the diagnosis of right sided thrombi. In this case early surgical intervention and removal of the thrombus might have altered the outcome. We believe that in such cases urgent surgical intervention should be considered at an early stage in an effort to avoid pulmonary embolism and its complications. Although right sided thrombi are uncommon and a very rare cause of pacemaker malfunction, cross sectional echocardiography may be useful, as in this case, in instances of otherwise unexplained intermittent pacemaker failure.

References

1 Haiderer O, Prager H, Koller H, Sterz H. Phlebographic findings after insertion of permanent pacemaker electrodes via the cephalic vein. In: Kumura E, Wathnabe Y, eds. *Vth International symposium on cardiac pacing*. Tokyo, 1976:5.

2 Mitrovic V, Thormanos J, Schleprer M, Neuss H. Thrombotic complications with pacemakers. *Int J Cardiol* 1983;2:363–74.

3 Nicolosi GL, Charmet PA, Zanuttini D. Large right atrial thrombosis: rare complication during permanent transvenous endocardial pacing. *Br Heart J* 1980;43:199–201.

4 Bogart DB, Collins RH, Montgomery MA, Dombek SJ, Earnest JB, Fischer EH. Shock late after implantation of permanent transvenous cardiac pacemaker. *Am J Cardiol* 1985;55:1241–2.

5 Wei JY, Hutchins GM, Bulkley BH. Papillary muscle rupture in fatal acute myocardial infarction. *Ann Intern Med* 1979;**90**:149–57.

6 Vlodaver Z, Edwards JE. Rupture of ventricular septum or papillary muscle complicating myocardial infarction. *Circulation* 1977;55:815–24.

7 Rosenzweig MS, Nada NC. Two dimensional echocardiographic detection of circulating right atrial thrombi. *Am Heart J* 1982;**103**:435–6.

8 Starky IR, De Bono DP. Endocardiographic identification of right-sided cardiac intracavitary thromboembolus in massive pulmonary embolism. *Circulation* 1982;**66**:1322–5.

9 Shiu MF, Abrams LD. Echocardiographic features of free floating thrombus mimicking right ventricular myxoma. *Br Heart J* 1983;49:612–4.

10 Chiarella F, Lupi G, Vecchio C. Early echocardiographic detection of right-sided intracardiac thrombus. *Int J Cardiol* 1986;**11**:121–4.

11 Brown AK, Anderson V. Resolution of right atrial thrombus shown by serial cross sectional echocardiography. *Br Heart J* 1985;53:659–61.

12 Come PC. Transient right atrial thrombus during acute myocardial infarction. *Am J Cardiol* 1983;**51**:1228–9.

13 Felner JM, Churchwell AL, Murphy DA. Right atrial thromboemboli: clinical echocardiographic and pathophysiological manifestations. *J Am Coll Cardiol* 1984;**4**:1041–51.

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A case of heterozygous Fabry's disease with a short PR interval and giant negative T waves

AKIHIRO YOKOYAMA, MASARU YAMAZOE, AKIRA SHIBATA

From the First Department of Internal Medicine, Niigata University School of Medicine, Niigata, Japan

SUMMARY A 55 year old woman with heterozygous Fabry's disease presented with cardiac symptoms. The electrocardiogram showed a PR interval of 0·12 s and giant negative T waves, suggesting apical hypertrophic cardiomyopathy. Endomyocardial biopsy, however, revealed myelin like substances characteristic of Fabry's disease. Increasing thickness of the left ventricular wall was seen by echocardiography over a period of five years. A deficiency of α galactosidase activity in the leucocytes confirmed the diagnosis of Fabry's disease, although this patient had neither angiokeratoma or proteinuria.

The possibility of Fabry's disease should be considered in patients with cardiomegaly of unknown cause and the following electrocardiographic abnormalities: *(a)* a PR interval ≤0·12 s, *(b)* high voltage QRS complexes in the left precordial leads, and *(c)* giant negative T waves.

Fabry's disease is a sex linked recessive disease. Heterozygous female cases seldom show overt symptoms,[1] and there are no previous reports of any presenting with cardiac symptoms. We report a case of heterozygous Fabry's disease that was confirmed by endomyocardial biopsy.

Case report

A 50 year old woman was admitted to the hospital of Niigata University School of Medicine in November 1980. She had complained of anterior chest pain and easy fatigability since the summer of that year.

On physical examination we found no dermatological abnormality. Her blood pressure was 126/60 mm Hg. Heart sounds were normal and no heart murmur was audible. There was no ankle oedema. The electrocardiogram showed a PR interval of 0·12 s and giant negative T waves in leads V5 and V6 (fig 1a). The chest radiograph showed no abnormality and the cardiothoracic ratio was 0·46. On M mode echocardiogram the thicknesses of the interventricular septum and the left ventricular posterior wall were 0·9 and 1·0 cm respectively (fig 2). Cross sectional echocardiography showed slight hypertrophy of the left ventricular apical area. There was no proteinuria. Concentrations of serum urea nitrogen and serum creatinine were 14 mg/dl and 0·8 mg/dl respectively.

Because the electrocardiographic findings were suggestive of apical hypertrophic cardiomyopathy we performed right and left heart catheterisation. The cardiac index was 2·9 l/min/m² and left ventricular end diastolic pressure was 4 mm Hg. Coronary angiography showed no significant obstructive lesion. The left ventricular angiogram showed slight hypertrophy of the wall of the apical area. The left ventricular ejection fraction was normal (78%). Endomyocardial biopsy of the right side of the intraventricular septum showed slight hypertrophy (mean 19 μm) and a focal mild degree of disarray of muscle cells. In about two thirds of the muscle cells granules or ring like deposits staining with toluidine blue and basic fuchsin were present both in the perinuclear zone and between myofibrils. In plastic embedded material the granules were demonstrable by the Kurotaki method[2] and electron microscopy confirmed the presence of myelinoid lamellar inclusions. The biopsy findings were those of Fabry's disease.[3 4]

The patient did not visit our hospital for five years,

Requests for reprints to Dr Akihiro Yokoyama, The First Department of Internal Medicine, 1-754 Asahimachi, Niigata 951, Japan.

but early in the summer of 1985 her anterior chest pain and easy fatigability became severe, with additional attacks of pain in the legs. She was readmitted to hospital in October with a one month history of fever. On physical examination, dry rales were heard at the base of both lungs and a fourth heart sound was audible. There was no ankle oedema. The chest *x* ray showed reticular shadows in both lower lung fields that were compatible with interstitial pneumonitis. The cardiothoracic ratio was 0·54 and slight cardiomegaly was seen. The electrocardiogram showed that septal Q waves, present on the electrocardiogram five years before (fig 1b), had disappeared. The echocardiogram showed that thickening of the interventricular septal wall and the posterior wall had increased to 1·4 and 1·5 cm respectively, with hypertrophy of the left ventricular wall, although there was no dilatation of the left ventricle (fig 2b). Her interstitial pneumonitis advanced and was accompanied with generalised convulsions and evidence of disseminated intravascular coagulation. The patient eventually died 32 days after admission to hospital.

At necropsy the heart weighed 540 g and the left ventricle showed concentric hypertrophy. There was hypertrophy and fibrosis of the myocardium, particularly in the ventricular septum. These findings are compatible with hypertrophy of the ventricular wall.

Alpha galactosidase activity was assayed by a fluorescence method with 4-meltylumbellibryl-D-galactopyranoside (Koch-Light) as a substrate. The α galactosidase activity of her leucocytes was 12·4 nmol/mg protein (normal (mean (SD)) 67·9 (16·2)).[5]

The patient's 27 year old daughter was found to be a carrier of the disease, although she was symptom free. Her electrocardiogram showed ST-T changes in leads II, III, and aVF.

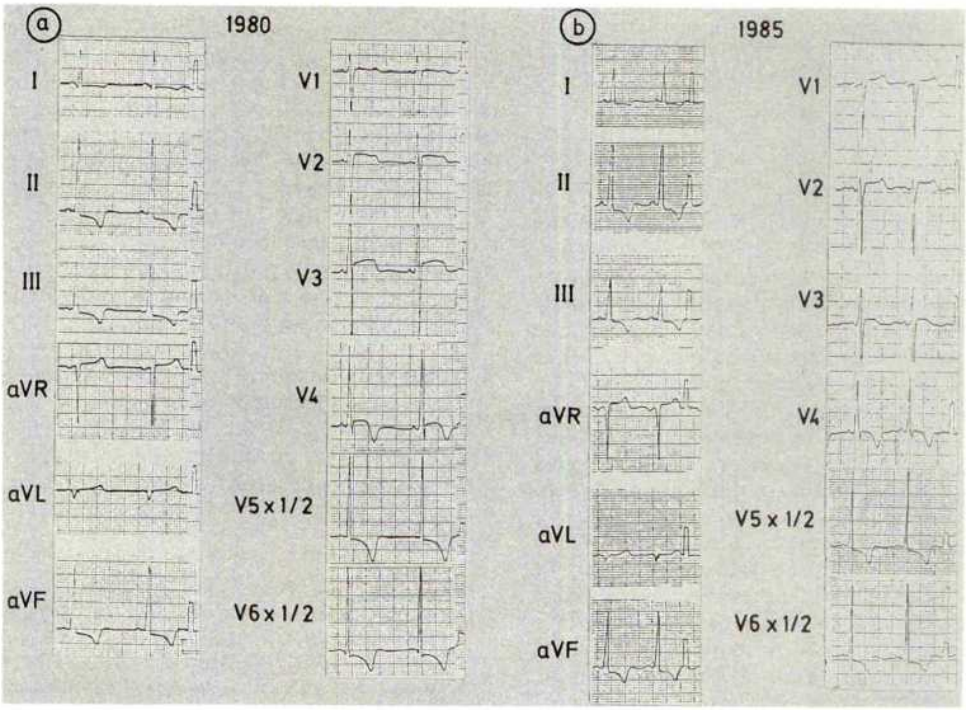

Fig 1 *An electrocardiogram. (a) recorded in 1980 showing a PR interval of 0·12 s and giant negative T waves in leads V5 and V6. There is no septal Q wave on the electrocardiogram (b) recorded in 1985; this was present 5 years before.*

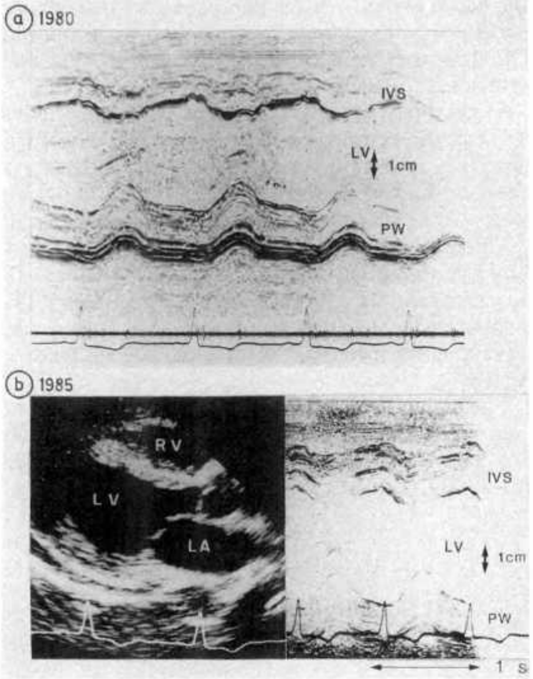

Fig 2 *An M mode echocardiogram taken in 1980 (a) and a cross sectional and M mode echocardiogram taken in 1985. LA, left atrium; LV, left ventricular cavity; IVS, interventricular septum; PW, posterior wall; RV, right ventricular cavity.*

Discussion

The reported incidence of Fabry's disease in the United States is 1 in 40 000. The disease is known to show multiple clinical manifestations related to deposits of ceramide trihexoside and ceramide in the systemic organs. Its clinical manifestations include angiokeratoma, proteinuria, and oedema of the lower legs and eyelids. It is a sex linked recessive condition and the heterozygous type when it occurs in females is rarely clinically apparent, with corneal symptoms alone being observed in most cases.[1] Female patients with Fabry's disease showing cardiac involvement are uncommon. Burda *et al* first reported a case of Fabry's disease with cardiovascular disorder as the main symptom.[6 7] They described a 47 year old woman who died of renal and cardiac insufficiency. Since then two cases in which there were cardiac manifestations have been enzymologically studied.[3 8] In these cases, however, hemizygotic Fabry's disease was diagnosed from the dermal findings, proteinuria, and family history. The mechanism of the occurrence of Fabry's disease as a sex linked recessive hereditary condition in females had been explained by the hypothesis of Lyon which states that one of the two X chromosomes in the cell is activated while the other is inactivated.[9] Indeed, Romeo and Migeon demonstrated two types of clone, one with normal α galactosidase activity and one with reduced α galactosidase activity in cultured skin fibroblasts from a patient with heterozygous Fabry's disease.[10]

The patient presented in this report had electrocardiographic findings suggestive of apical hypertrophic cardiomyopathy.[11 12] The echocardiograms and left ventriculograms obtained in 1980 showed only mild hypertrophy of the left ventricular apical wall, and Fabry's disease was first suspected because of the results of endomyocardial biopsy. The serial M mode echocardiograms showed increases in the thickness of the interventricular septum from 0·9 to 1·4 cm and the left ventricular posterior wall from 1·0 to 1·5 cm. The cross sectional echocardiograms obtained in 1985 also showed considerable concentric hypertrophy of the left ventricle. There has been no previous report describing such a progression of cardiac findings in Fabry's disease.

It has been reported that the PR interval is often ≤0·12 s in Fabry's disease.[13 14] According to Matsui *et al*,[8] the mechanism of this short PR interval is an electrophysiologically accelerated conduction through the atrioventricular node, possibly caused by adherence of glycolipids to the atrioventricular node. It is interesting that the PR interval is short in patients with Pompe's disease—that is glycogenosis. None the less, there has been no report of an association between apical hypertrophic cardiomyopathy with giant negative T wave and a PR interval ≤0·12 s. Therefore, if both these findings, a PR interval ≤0·12 s and giant negative T wave, are seen together, it raises the possibility of Fabry's disease, even, as in the present patient, in the absence of angiokeratoma or nephrotic disorder.

We thank Dr I Hozumi, Dr M Nishizawa, and Dr T Miyatake who measured the activities of α galactosidase; Dr T Izumi and Dr F Masani who performed part of the endomyocardial biopsy; and Dr D G Gibson, for help in preparing the manuscript.

References

1 Desnic RJ, Sweeley CC. Fabry's disease (α-galactosidase A deficiency). In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. *The metabolic basis of inherited disease*. New York: MacGraw-Hill, 1983:906–44.
2 Kurotaki M. A differential staining of semithin sections of epon-embedded tissue and a short review on the optical microscopy of plastic-embedded tissue. *Acta anat Nippon* 1972;**47**:237–50.
3 Broadbent JC, Edwards WD, Gordon H, Hartzler GO,

Krawisz JE. Fabry cardiomyopathy in the female confirmed by endomyocardial biopsy *Mayo Clin Proc* 1981;**56**:623–8
4 Rodorignez FH, Hoffmann EO, Ordinario AT, Baliga M. Fabry's in a heterozygous women. *Arch Pathol Lab Med* 1985;**109**:89–92.
5 Suzuki K. Enzymic diagnosis of sphingolipidosis. In: Ginsburg V, ed. *Methods in enzymology*. Vol 50. New York. Academic Press, 1978:456–98.
6 Burda CD, Winder PR. Angiokeratoma corpus diffusum universale in female subjects. *Am J Med* 1967;**42**:293–301.
7 Burda CD. The heart in Fabry's disease. *Am J Cardiol* 1969;**24**:95–110.
8 Matsui S, Murakami E, Takekoshi N, *et al* Cardiac manifestations of Fabry's disease Report of a case with pulmonary regurgitation diagnosed on the basis of endomyocardial biopsy findings *Jpn Circ J* 1977;**41**:1023–36.
9 Lyon MG. Gene action in the X-chromosome of the mouse. *Nature* 1961;**190** 372–84.
10 Romeo G, Migeon BR. Genetic activation of the α-galactosidase locus in carriers of Fabry's disease. *Science* 1970;**170**:180–1.
11 Sakamoto T, Tei C, Murayama M, *et al.* Giant negative T wave inversion as a manifestation of asymmetric apical hypertrophy (AAH) of the left ventricle. Echocardiographic and ultrasonocardiographic study. *Jpn Heart J* 1976;**17**·611–9.
12 Yamaguchi H, Ishimura T, Nishiyama S, *et al* Hypertrophic nonobstructive cardiomyopathy with giant negative T waves (apical hypertrophy): ventriculographic and echocardiographic features in 30 patients. *Am J Cardiol* 1979;**44**:401–12
13 Roudebush CP, Foerster JM, Bing OHL. The abbreviated PR interval of Fabry's disease [Abstract]. *Circulation* 1973;**48**(suppl IV):IV–210
14 Mehta J, Tuna N, Moller JH, Densnick RJ. Electrocardiographic and vectorcardiographic abnormalities in Fabry's disease. *Am Heart J* 1977;**93**:669–76.

Notices

British Cardiac Society

The Annual General Meeting for 1987 will take place in Dundee on 8 and 9 April 1987, and the closing date for receipt of abstracts was 6 January 1987.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

Pacing and electrophysiology

The 8th Annual Scientific Session, North American Society of Pacing and Electrophysiology will take place in Boston on 30 April to 3 May 1987. Further details from: NASPE, 13 Eaton Court, Wellesley Hills, MA 02181, USA.

Heart research

The 9th Annual Meeting of the International Society of Heart Research (ISHR), American Section, will be held in Boston on 8 to 12 September 1987. Inquiries to: Dr Joanne S Ingwall, Director, NMR Laboratory, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA.

Br Heart J 1987;**57**:300

Correspondence

Unusual echocardiographic appearance of intracardiac thrombi in a patient with endomyocardial fibrosis

Sir,

We were interested to read the report by Wiseman *et al* (1986;**56**:179–81) describing a patient with intracardiac thrombi which had echolucent centres.

We recently encountered a similar echocardiographic appearance in a 72 year old woman admitted with cardiac failure. Cross sectional echocardiography showed biventricular dilatation with uniformly reduced ventricular function that was compatible with a congestive cardiomyopathy. A spherical mass with a thin echogenic perimeter and a large echolucent centre was seen to be attached to the anteroseptal wall of the left ventricle just below the level of the papillary muscles. Although cardiac tumours can have small echolucent areas, we felt that the position and the clinical setting of this lesion made ventricular thrombus with liquefaction at its centre the most likely diagnosis. Despite anticoagulation the patient sustained a left sided hemiplegia ten days after admission and repeat echocardiography showed the lesion to be smaller and uniformly echodense. We believe that the echocardiographic findings were the result of a thrombus with a liquefied centre which subsequently became partly embolised. The histology in the case reported by Wiseman *et al* lends support to our presumptive diagnosis.

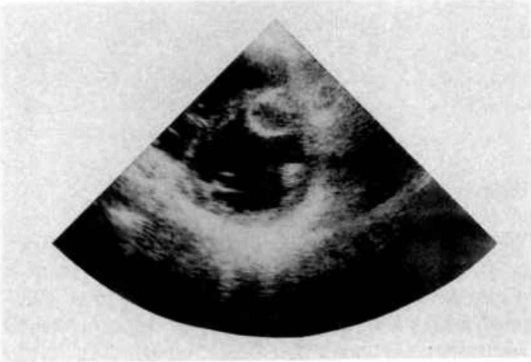

Figure *Echocardiogram in the parasternal short axis view at the level of the papillary muscles showing the mass with an echolucent centre.*

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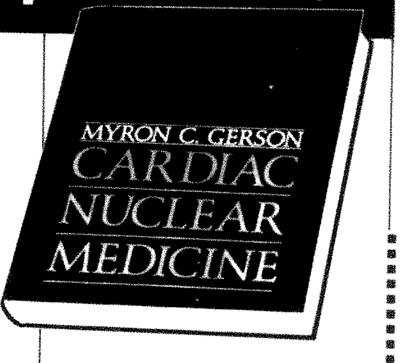

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Presentation

Transiderm-Nitro 5 patches containing a drug reservoir of 25mg glyceryl trinitrate (average amount of glyceryl trinitrate absorbed per patch in 24 hours is 5mg). Transiderm-Nitro 10 patches containing 50mg glyceryl trinitrate (average of 10mg absorbed per patch in 24 hours).

Indications

Prophylactic treatment of attacks of angina pectoris.

Dosage and administration

One Transiderm-Nitro 5 patch is to be applied every 24 hours. If a higher dose is required, a Transiderm-Nitro 10 patch may be substituted. Apply patch to lateral chest wall. Remove patch after 24 hours, apply replacement patch to new area of skin. Acute attacks of angina may require rapid-acting nitrate preparations.

Side-effects

Headache, reflex tachycardia, postural hypotension, nausea, dizziness and allergic skin reactions.

Precautions

Recent myocardial infarction, acute heart failure, gradual withdrawal of treatment, pregnancy. The system should be removed before cardioversion or DC defibrillation is attempted.

Contra-indications

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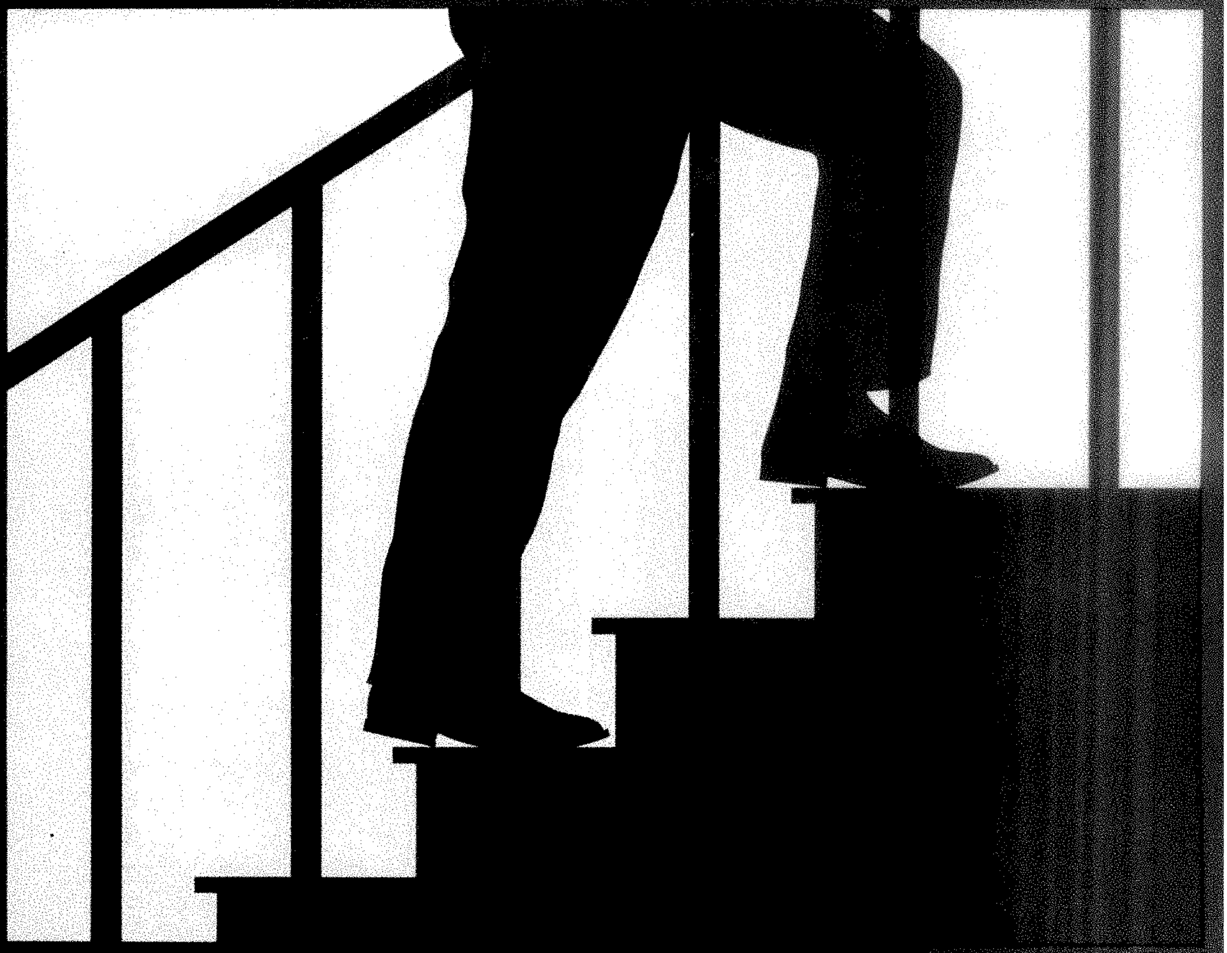
Full prescribing information is available on request from CIBA Laboratories, Horsham, West Sussex.



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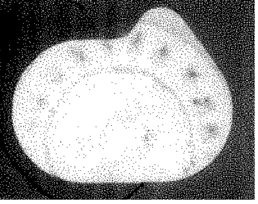

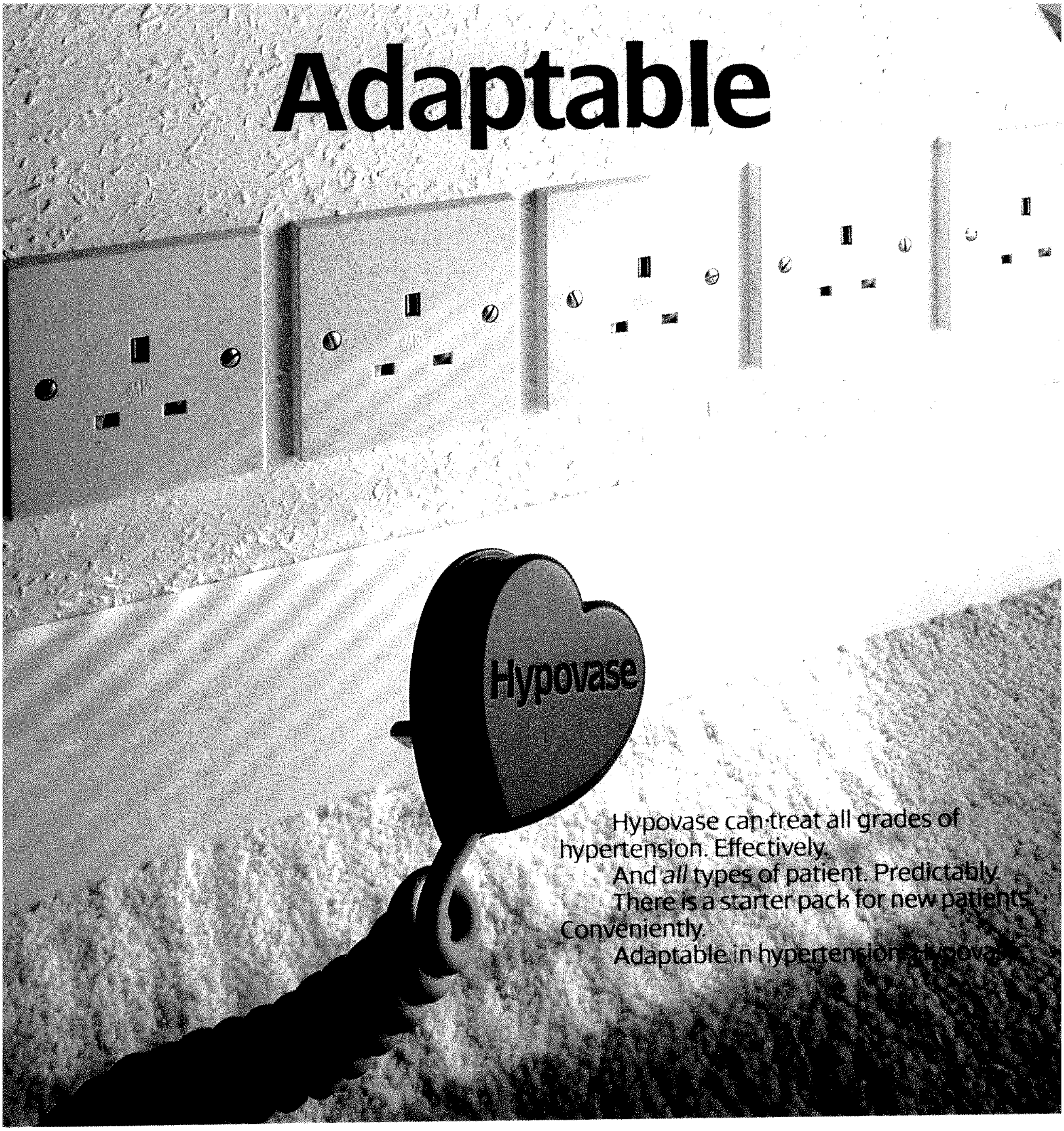
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Jubilee Editorial

Coronary thrombolysis

DAVID DE BONO

From the Department of Cardiology, Royal Infirmary of Edinburgh

Fifty years ago, when the Cardiac Society of Great Britain and Ireland was founded, myocardial infarction was a well recognised, but hardly a commonplace, diagnosis. A quarter century before, Obrastzow and Straschenko,[1] and then Herrick,[2] had recognised the clinical syndrome of coronary thrombosis, and in the intervening years Pardee,[3] Parkinson and Bedford,[4] and Wilson *et. al*[5] had defined the crucial role of electrocardiography in diagnosis. Yet Gilchrist, president of the Cardiac Society in its foundation year, had diagnosed the first case of myocardial infarction to be recognised in the Royal Infirmary of Edinburgh less than a decade earlier. It could be argued that in any event diagnosis of myocardial infarction in 1937 was of prognostic, rather than therapeutic, importance, because apart from analgesia and bed rest (for at least a month, very strict for the first fortnight[6]) there was little else to offer: quinidine for ventricular arrhythmias; digitalis for atrial fibrillation; mercurial diuretics. There were no bedside monitors, defibrillators, β blockers, or loop diuretics. Yet, ironically, Tillett and Garner had already identified the fibrinolytic activity of streptococci,[7] heparin was in use for venous thrombosis,[8] and within five years coumarin anticoagulants would have their first trials.[9] It took another twenty years before these concepts were first assembled into a fundamental attack on the immediate cause of infarction.[10]

How does it work?

Coronary thrombosis, usually at the site of a ruptured atheromatous plaque, causes the majority of acute myocardial infarcts.[11-13] The thrombus can be dissolved by intracoronary or intravenous administration of thrombolytic drugs without causing unacceptable bleeding complications.[14-16] Assessment of success in restoring coronary patency is complicated by spontaneous reperfusion.[17 18] Coronary patency rates assessed by a single angiogram 90 minutes after thrombolytic treatment are usually 15–20% higher than reperfusion rates in vessels shown by pretreatment angiography to be occluded. On the other hand, the delay introduced by pretreatment angiography may reduce the likelihood of successful thrombolysis. The patency rate associated with intravenous streptokinase is probably in the range 55–75% if treatment is given during the critical period when limitation of myocardial damage is possible.[16] About 70% of reperfused vessels are left with a significant degree of coronary stenosis at the site of initial occlusion.[19 20] The rate of early reocclusion is high in vessels with a very tight residual stenosis,[21] but it is arguable whether the limited amount of blood flow that such vessels provide is of much value in maintaining myocardial viability. In patients with lesser degrees of obstruction the severity of the residual stenosis tends to diminish with time.[22]

Estimates of reocclusion rates after coronary thrombolysis range from 12% to 40%.[16 23] There was clinical or angiographic evidence (or both) of reocclusion in 15% of the first 80 patients treated in Edinburgh who were followed up for a year or longer. Half the reocclusions occurred within the first week and three quarters within the first month.

Is it worth while?

Does coronary thrombolysis improve outcome in terms of survival and ventricular function, and which patients should have thrombolysis? Early trials were too small to answer these questions or not

Requests for reprints to Dr David de Bono, Department of Cardiology, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW

designed to answer them. A pooled overview by Yusuf and colleagues suggested an increase in survival of 10–15% that was independent of any treatment delay within the first 24 hours,[24] but more recent large individual studies give a different view. In the GISSI study 11 806 patients (out of 31 826 screened for entry) were randomised to receive either placebo or 1 500 000 units of streptokinase infused over an hour.[25] Twenty one day survival was 10·7% in the treated group and 13·0% in the untreated group ($p < 0·0002$)—a reduction in mortality of 17%. Prospective stratification according to the delay between time of onset and symptoms indicated that the effect was almost entirely the result of improved survival in the groups treated within three hours of infarction (9 2% *vs* 12%) or between three and six hours (11·7 *vs* 14 1%). When the results in over 1000 patients treated within one hour were analysed an even greater effect was found—mortality was 8·2% in the treated group and 15·4% in the untreated group, an improvement of 46% in the chances of survival.

The Netherlands interuniversity study confirmed the importance of early treatment in 533 patients randomised to a control group or a streptokinase group with or without coronary angioplasty. Infarct size (measured by plasma hydroxybutyrate dehydrogenase activity) was reduced by 51% in patients treated within an hour, by 31% in those treated between one and two hours, and by 13% in those treated between two and four hours.[26] Left ventricular ejection fraction, measured by predischarge cineangiography, was higher after thrombolysis both in patients with anterior infarcts and in those with inferior infarcts.[27]

The measurement of left ventricular function after infarction and thrombolysis is complex and results depend on the technique used and the time it is applied. Gated blood pool radionuclide ventriculography probably underestimates the effects of inferior infarction, whereas cineangiography must take account of changes in phase of left ventricular wall movement as well as changes in amplitude. In the GISSI study the reduction in mortality was most pronounced in those with anterior infarction—survival after inferior infarction was good in both the treated and untreated groups. Improved survival was also more likely after first infarcts than after recurrent infarcts, perhaps because these are associated with reduced myocardial reserve and need more effective restoration of perfusion than that provided by the GISSI protocol. The importance of early treatment in preserving myocardial function accords with laboratory studies of the rate of myocardial necrosis after coronary occlusion.[28] Very early treatment may not only limit infarction but may also prevent it.[29 30]

Who should get thrombolytic treatment?

The most obvious message coming from these clinical trials is that patients with anterior infarcts who have had major symptoms for less than three hours are the most likely to benefit. Clinical trials may produce their own artefacts, however, and uncertainty over the duration of symptoms may exclude patients with "stuttering" infarction who might benefit particularly. Global measurements of left ventricular function are also more sensitive to anteroapical akinesis than to the changes induced by right coronary artery occlusion. At present, it seems reasonable to propose that whatever the duration of symptoms patients with persistent ischaemic chest pain and ST elevation that are unresponsive to nitrates and patients with unstable angina and angiographically demonstrated intracoronary thrombus should be considered for thrombolysis.

The main contraindication to coronary thrombolysis is a risk of haemorrhage because of known peptic ulceration, head injury, traumatic resuscitation, or recent surgery. The individual risks must be weighed against the potential benefits.

How should it be done?

For practical reasons the intravenous route is much more widely applicable than the intracoronary one.[31] Streptokinase is by far the most widely used thrombolytic drug. The cost of urokinase in many countries remains prohibitive, but its relative lack of antigenicity may be useful for repeated treatments. Tissue plasminogen activator[32–34] and acylated plasminogen streptokinase complex (APSAC) (BRL 26921, Eminase)[35] are likely to be marketed in some countries in the near future, but at present they are available only for use in research studies. The most popular regimen for giving intravenous streptokinase is that developed by Schroder and colleagues[15] from the original "high dose, short time" concept of Breddin *et al.*[36] 1 500 000 units of streptokinase are given intravenously over 60 minutes in 100 ml of 5% glucose. This may be preceded by chlorpheniramine 10 mg and a steroid—for example hydrocortisone 100 mg—to suppress allergic reactions. The possible role of platelets has been acknowledged in some regimens in which aspirin (100–300 mg) is given orally or intravenously (no parenteral aspirin preparation is currently available in the United Kingdom). Thrombolytic treatment should not distract attention from good medical care with analgesia, arrhythmia monitoring, and treatment of cardiac failure. Short term β blockade may help to protect the myocardium during thrombolysis, and this treatment is currently being evaluated in at least two trials. Nitrates on their own are seldom effective in restoring coronary patency, but they may improve and maintain patency induced by thrombolysis.[29] On the other hand, excessive doses of nitrates may produce deleterious haemodynamic effects, especially in inferior infarction.

Indiscriminate venepuncture should be forbidden, and a single cannula is usually sufficient for blood sampling and drug administration. If they are needed, pacemaker electrodes or Swan-Ganz catheters should be inserted via an antecubital or femoral vein: subclavian puncture is safer once the initial wave of thrombolysis has passed. In about 50% of patients in whom an occluded vessel is reperfused this will be signalled by an arrhythmia—usually a short burst of idioventricular rhythm, but 5–10% will have ventricular tachycardia or fibrillation. Most, but not all, patients show a reduction in ST segment elevation.

Follow up after thrombolysis

Ideally an intravenous thrombolytic agent should be given as early as possible after infarction—perhaps at home or in an ambulance—and on arrival at hospital the patient should be taken immediately to the catheter laboratory.[26 27] If the infarct related vessel is not adequately perfused, mechanical perforation with a guide wire or immediate angioplasty or both can be done. It can be argued[37 38] that immediate angioplasty of a residual stenosis in a patent vessel will improve perfusion and help preserve the myocardium, but this remains to be tested in controlled trials.

Even if coronary angiography or angioplasty facilities are not immediately available it is worth while to give intravenous thrombolytic treatment. Reperfusion can often be inferred from relief of pain, reperfusion arrhythmias, sudden reduction of ST elevation, and a rapid release pattern of plasma creatine kinase activity. Patients whose condition remains unstable with recurring pain and fluctuating ST elevation should be transferred for emergency angiography; the remainder can have elective angiography later. There is no answer yet to the question of whether subsequent intervention in the latter group should be based on angiographic appearances or on evidence of persisting myocardial ischaemia such as angina, a positive exercise test, or perfusion scanning.

Our present policy is to perform elective coronary angiography four to six weeks after infarction in patients who have post-infarct angina or who are limited by symptoms to less than five minutes' exercise on a standard Bruce protocol. We refer patients for angioplasty or bypass grafting according to the angiographic appearances. Using these criteria, which are similar to those we use for post-infarction patients who have not had thrombolysis,[39 40] we refer approximately 25% of post-thrombolysis patients for coronary angioplasty or bypass grafting within a year of treatment. This proportion is similar to the intervention rate reported by the Belfast group.[41] In their view, however, elective angiography should be performed in all patients. Many practitioners of thrombolysis believe that anticoagulation, at least for the first month after thrombolysis, is important in preventing reocclusion—but unfortunately evidence for this tends to be anecdotal rather than based on the results of comparative trials. It is our policy to anticoagulate with heparin for three days followed by warfarin for up to three months. The current Intravenous Short Term Infusion of Streptokinase and GISSI 2 trials may provide more evidence for or against the importance of anticoagulation, and paradoxically anticoagulation may prove to be more important with the more thrombus selective agents than with streptokinase.

What proportion of myocardial infarct patients should have thrombolytic treatment?

Murray *et al* concluded that only a small proportion of patients admitted to a London coronary care unit fulfilled the criteria for thrombolytic treatment.[42] Jagger and colleagues from Birmingham were more optimistic, and reckoned that thrombolysis would have been suitable for 50% of admissions.[43] There are two problems with this type of study; first, the rigid entry criteria that are appropriate for a clinical trial of a new drug may not be so appropriate for therapeutic use. Second, the denominator should really be the number of patients having infarcts in the community—which is much more difficult to measure than the number of admissions. Several clinical trials are under way to study methods of administering thrombolytic treatment before hospital admission. Their results may provide a further incentive for the establishment and funding of rapid response or rapid admission schemes, which will need to be tailored to individual local requirements.

References

1 Obrastzow WP, Straschenko ND. Zur Kenntnis der Thrombose der Koronararterien des Herzens. *Z Klin Med* 1910;71:116–25.

2 Herrick JB. Clinical features of sudden obstruction of the coronary arteries. *JAMA* 1912;59:2015–20.

3 Pardee HEB. An electrocardiographic sign of coronary artery obstruction. *Arch Intern Med* 1920;**26**: 244–50.

4 Parkinson J, Bedford DE. Successive changes in the electrocardiogram after cardiac infarction (coronary thrombosis). *Heart* 1928;**14**:195–240.

5 Wilson FN, Macleod, AG, Barker PS, Johnstone FD, Klostermeyer LL. The electrocardiogram in myocardial infarction with particular reference to the initial deflection of the ventricular complex. *Heart* 1933;**16**:155–99.

6 White PD. *Heart disease*. 3rd ed. New York: Macmillan, 1945: 501.

7 Tillett WS, Garner RL. The fibrinolytic activity of haemolytic streptococci. *J Exp Med* 1933;**58**: 485–502.

8 Murray DWG, Jaques LB, Perrett TS, Best CH. Heparin and the thrombosis of veins following surgery. *Surgery* 1937;**2**:163–87.

9 Allen EW, Barker WW, Waugh JM. A preparation from spoiled sweet clover which prolongs coagulation and prothrombin time of the blood. *JAMA* 1942;**120**:1009–21.

10 Fletcher AP, Alkjaersig N, Smyrniotis FE, Sherry S. The treatment of patients suffering from early myocardial infarction with massive and prolonged streptokinase therapy. *Trans Assoc Am Physicians* 1958;**71**:287–95.

11 Fulton WFM. The morphology of the coronary thrombotic occlusions relevant to thrombolytic intervention. In: Kaltenbach M, Gruntzig A, Rentrop K, Bussmann WD, eds. *Transluminal coronary angioplasty and coronary thrombolysis*. Berlin, Heidelberg, New York. Springer-Verlag, 1982:244–52.

12 Silver MD, Baroldi G, Mariani F. The relationship between acute occlusive coronary thrombi and myocardial infarction studied in 100 consecutive patients. *Circulation* 1980;**61**:219–27.

13 Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J* 1985;**53**: 363–73.

14 Rentrop P, de Vivie ER, Karsh KR, Kreuzer H. Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase in combination with transluminal recanalisation. *Clin Cardiol* 1979;**5**: 354–6.

15 Schroder R, Biamino G, von Leitner ER, *et al*. Intravenous short term infusion of streptokinase in acute myocardial infarction. *Circulation* 1983;**67**:536–47.

16 Rentrop KP. Thrombolytic therapy in patients with acute myocardial infarction. *Circulation* 1985;**71**: 627–31.

17 De Wood MA, Spores J, Notske R, *et al*. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;**303**:897–902.

18 Rentrop P, Feit F, Blanke H, *et al*. Effects of intracoronary streptokinase and intracoronary nitroglycerin infusion on coronary angiographic patterns and mortality in patients with acute myocardial infarction. *N Engl J Med* 1984;**311**:1464–8.

19 Serruys PW, Wijns W, van den Brand M, *et al*. Is transluminal coronary angioplasty mandatory after successful thrombolysis? Quantitative coronary angiographic study. *Br Heart J* 1983;**50**:257–65.

20 Uebis R, von Essen R, Schmidt WG, Franke A, Effert S. Reststenose nach erfolgreicher selectiver Lyse kompletter thrombotischer Koronararterienverschluesse beim akuten Myocardinfarkt. *Z Kardiol* 1985;**74**:519–24.

21 Harrison DG, Ferguson DW, Collins SM, *et al*. Rethrombosis after reperfusion with streptokinase: importance of geometry of individual lesions. *Circulation* 1984;**69**:991–6

22 Cribier A, Saudi N, Berland J, Letac B. Regression of residual coronary stenosis after recanalization by fibrinolysis in myocardial infarction. Quantitative analysis of coronary angiography immediately after obstruction removal, at a 15 day and 3 month follow up. *Arch Mal Coeur* 1985;**78**:353–60.

23 Ward Kennedy J, Ritchie JL, Davis KB, *et al*. The Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction: a 12 month follow up report. *N Engl J Med* 1985;**312**:1073–7.

24 Yusuf S, Collins R, Peto R, *et al*. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction and side effects from 33 randomized controlled trials. *Eur Heart J* 1985;**6**:556–85.

25 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**i**:397–401.

26 Simoons ML, Serruys PW, van den Brand M, *et al*. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. *J Am Coll Cardiol* 1986;**7**:717–28.

27 Serruys PW, Simoons ML, Suryapranata H, *et al*. Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 1986;**7**:729–42.

28 Jennings RB, Reimer KA. Factors involved in salvaging ischaemic myocardium: effect of reperfusion of arterial blood. *Circulation* 1985;**68**(suppl 1):25–36.

29 Davies GJ, Chierchia S, Maseri A. Prevention of myocardial infarction by very early treatment with intracoronary streptokinase. *N Engl J Med* 1984; **311**:1468–92.

30 Koren G, Weiss AI, Hosin Y, *et al*. Prevention of myocardial damage in acute myocardial infarction by early treatment with intravenous streptokinase. *N Engl J Med* 1985;**313**:1384–9.

31 Verstraete M. Intravenous administration of a thrombolytic agent is the only realistic therapeutic approach in myocardial infarction. *Eur Heart J* 1985;**6**:586–93.

32 The TIMI Study Group. The thrombolysis in myocardial infarction (TIMI) study. *N Engl J Med* 1985;**312**:932–6.

33 Verstraete M, Bernard R, Bory M, *et al*. Randomized trial of intravenous recombinant tissue type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. *Lancet* 1985;**i**:842–7.

34 Verstraete M, Bleifeld W, Brower RW, *et al*. Double

blind randomized trial of intravenous recombinant tissue type plasminogen activator versus placebo in acute myocardial infarction. *Lancet* 1985;ii:965–9.

35 Been M, de Bono DP, Muir AL, *et al.* Clinical effects and kinetic properties of intravenous APSAC—anisoylated plasminogen-streptokinase activator complex (BRL 26921) in acute myocardial infarction. *Int J Cardiol* 1986;11:53–61.

36 Breddin K, Ehrly AM, Fechler L, *et al.* Die Kurtzeit Fibrinolyse beim akuten Myokardinfarkt. *Dtsch Med Wochenschr* 1973,98:861–73.

37 Meyer J, Merx W, Schmitz H, *et al.* Percutaneous transluminal coronary angioplasty immediately after intracoronary streptolysis of transmural myocardial infarction. *Circulation* 1982;66:905–13.

38 Sheehan FH, Matthey DG, Schofer J, Dodge HT, Bolson EL. Factors determining recovery of left ventricular function following thrombolysis in myocardial infarction. *Circulation* 1985;71:1121–8.

39 Peart I, Seth L, Albers C, Odemuyiwa O, Hall RJC. Post-infarction exercise testing in patients under 55 years: relation between ischaemic abnormalities and the extent of coronary artery disease. *Br Heart J* 1986;55:67–74.

40 Veenbrink ThWG, van der Werf T, Westerhof PW, Robles de Medina EO, Meijler FL. Is there an indication for coronary arteriography in patients under 60 years of age with no or minimal angina pectoris after a first myocardial infarction? *Br Heart J* 1985;53:30–5.

41 MacLennan BA, McMaster A, Webb SW, Khan MM, Adgey AAJ. High dose intravenous streptokinase in acute myocardial infarction—short and long term prognosis. *Br Heart J* 1986;55:231–9

42 Murray N, Lyons J, Layton C, Balcon R. What proportion of patients with myocardial infarction are suitable for thrombolysis? *Br Heart J* 1987;57:144–7.

43 Jagger JD, Murray RG, Davies MK, Littler WA, Flint EJ. Eligibility for thrombolytic therapy in acute myocardial infarction. *Lancet* 1987;i:34–5.

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Prognostic value of predischarge 12 lead electrocardiogram after myocardial infarction compared with other routine clinical variables

PAOLO FIORETTI, JAN G P TIJSSEN, AIDA J AZAR, ETTORE LAZZERONI,*
R W BROWER,† HARALD J TEN KATEN,† JACOBUS LUBSEN,
PAUL G HUGENHOLTZ

*From the Thoraxcenter, Erasmus University, Rotterdam, the †Interuniversity Cardiology Institute, Rotterdam, the Netherlands, and *Divisione di Cardiologia, Ospedale Regionale, Parma, Italy*

SUMMARY The prognostic value of QRS score (Selvester), ST depression, ST elevation, extrasystoles, P terminal force in V1, and QTc derived from the predischarge 12 lead electrocardiogram was assessed after myocardial infarction in 474 patients without intraventricular conduction defects, ventricular hypertrophy, or atrial fibrillation. The usefulness of these results in risk assessment was compared with that of other clinical data. During follow up 45 patients died. Logistic regression analysis showed that QRS score, ST depression, and QTc were independently predictive of cardiac mortality. When multivariate analysis was applied to clinical and electrocardiographic data together, however, the 12 lead electrocardiogram did not provide independent information additional to that provided by other routine clinical findings and laboratory tests such as a history of previous myocardial infarction, clinical signs of persistent heart failure, indication for digitalis or antiarrhythmic drugs at discharge, and enlarged heart on chest *x* ray.

In conclusion, the electrocardiogram has important prognostic value; however, it is not powerful enough to further improve the risk assessment of post-infarction patients.

Some tests of cardiac function (mainly related to the detection of myocardial ischaemia, the quality of left ventricular function, or the occurrence of ventricular arrhythmias) have been used to assess risk after myocardial infarction. It is apparent that there is considerable overlap in the information derived from these tests.[1] Furthermore, because many hospitals cannot provide all these tests, which are expensive and in some cases risky for the patient, it is important to know how to make the best possible use of standard clinical and laboratory tests in risk assessments.

The 12 lead electrocardiogram is valuable in risk assessment in patients after myocardial infarction.[2-7] However, few studies have also determined the usefulness of other clinical findings[2] or have used a multivariate analysis for variables that predict mortality. The routine 12 lead electrocardiogram is an attractive tool for risk assessment in patients after infarction because it provides information on the extent of myocardial damage,[8] left atrium overload,[7 9] presence of myocardial ischaemia,[2 10] arrhythmias,[3] and electrical instability.[4 5]

The aim of this study was to analyse the power of different variables extracted from the predischarge electrocardiogram to predict one year survival after myocardial infarction and to establish whether they provide information that is additional to that supplied by routine clinical findings and tests. The study was based on 474 hospital survivors of myocardial infarction without intraventricular conduction defects, ventricular hypertrophy, or atrial fibrillation—all of which are markers of increased cardiac risk.

Requests for reprints to Dr Paolo Fioretti, Erasmus University, Thoraxcenter BD 373, PO Box 1738, 3000 DR Rotterdam, The Netherlands

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Table 1 *Data on the patients in whom clinical and electrocardiographic variables were studied*

	No	*1 year mortality*
Admitted with AMI	706	174 (25%)
Hospital deaths	104	104 (100%)
Discharged alive	602	72 (12%)
Excluded	128	27 (21%)
Lost to follow up	6	—
Non-cardiac death	2	2
Missing or bad quality predischarge ECG	36	3 (8%)
IVCD and/or VH and/or AF	84	22 (26%)
Study base	474	45 (9%)

AMI, acute myocardial infarction, ECG, 12 lead electrocardiogram, IVCD, intraventricular conduction defects; VH, ventricular hypertrophy, AF, atrial fibrillation.

Patients and methods

From March 1981 to December 1983, 706 patients were consecutively admitted to the coronary care unit of the Thoraxcenter with a confirmed diagnosis of acute myocardial infarction. Four hundred and seventy four of the 602 hospital survivors form the base for this study (table 1). All these patients were followed for one year, with death as the end point. Table 2 shows the differences in selected baseline characteristics between 474 patients included in the study and 84 patients excluded because they had intraventricular conduction defects, ventricular hypertrophy, or atrial fibrillation. We used two sets of information to predict mortality—one derived from the predischarge 12 lead electrocardiogram and another based on the remaining clinical and laboratory findings obtained in hospital.

ELECTROCARDIOGRAPHIC VARIABLES

At discharge the standard 12 lead electrocardiogram was obtained on a three channel Hewlett Packard 1513 A recorder at a paper speed of 25 mm/s. The following electrocardiographic variables were measured: the presence of ventricular extrasystoles, QRS score developed by Selvester,[8] ST depression (horizontal or downsloping) or elevation of $\geqslant$ 1 mm, P terminal force in V1,[7 9] and QT interval corrected for heart rate (QTc).[4 5] The measurements were performed by one cardiologist who was unaware of the outcome of the individual patients. In a previous study we showed that when the QRS score was measured agreement between two independent observers was good.[6]

OTHER CLINICAL VARIABLES

The other routine variables were age, sex, history of previous myocardial infarction, history of previous stable angina pectoris, peak serum creatine kinase, the worst Killip class while the patient was in the coronary care unit, early post-infarction angina, "late" ($\geqslant$ 72 hours after the onset of infarction) ventricular fibrillation, late sustained ventricular tachycardia or atrial arrhythmias, persistent heart failure after discharge from the coronary care unit, resting heart rate at discharge, cardiomegaly (cardiothoracic ratio > 50%), and signs of pulmonary congestion on predischarge chest *x* ray, and medication at discharge (digitalis, diuretics, β blockers, antiarrhythmics, anticoagulants). Selection of these variables was based on clinical experience and previous research in our clinic.

Other tests performed before discharge such as radionuclide ventriculography at rest (in 417 patients), symptom limited bicycle ergometry (in 340 patients), and 24 hour ambulatory electrocardiographic monitoring (in 310 patients), have been described elsewhere.[1] Cardiac catheterisation with coronary arteriography was performed in 235 patients as an elective procedure or as part of a randomised trial of intracoronary streptokinase.[11–13] Before discharge from hospital 46 patients had coronary artery bypass surgery, and 15 had percutaneous transluminal coronary angioplasty.

STATISTICAL ANALYSIS

Univariate analysis of the different electrocardiographic and clinical variables was performed. Continuous variables were divided into thirds. The 95% confidence intervals for the respective risk ratios were calculated according to Miettinen and Nurminen[10]; the first tertile was regarded as the reference group. If the 95% confidence interval exceeds 1, the association of the respective variable with the risk of dying within one year is statistically significant at the 5% level.

In the multivariate analysis the logistic regression model was used to predict mortality. Thus the objective was to find the combination of variables that most closely predicted mortality. As a general principle, we used indicator variables. These variables

Table 2 *Differences of selected baseline characteristics between patients in the study group and those excluded from the study because of ventricular conduction defects, atrial fibrillation, or ventricular hypertrophy*

	Study group	*Excluded*	*p value*
No of patients	474	84	—
Age (yr) mean (SD)	57 (11)	61 (10)	0 002
Previous AMI (No (%))	143 (30)	26 (33)	NS
Late heart failure (No (%))	63 (13)	27 (35)	0 0005
CTR > 50% (No (%))	95 (20)	34 (44)	0 0005
EF (% (mean (SD)))	47 (14)	37 (17)	0 0005
Extrasystoles (No (%))	19 (4)	6 (8)	NS
PTF (mm ms (mean (SD)))	20 (4)	26 (18)	0 0005

AMI, acute myocardial infarction; CTR, cardiothoracic ratio, EF, left ventricular ejection fraction, PTF, terminal force of P wave in V1.

Table 3 *Mortality, risk ratios, and confidence intervals for the different electrocardiographic and clinical variables determined by univariate analysis*

	No	*Mortality*	*Risk ratio*	*95% confidence interval*
		12 lead electrocardiogram		
QRS score:				
< 2	144	9 (6·3%)	—	—
2–5	140	10 (7·1%)	1·1	0·5–2·7
> 5	190	26 (13·7%)	2·2	1·1–4·5
ST segment depression				
No	414	34 (8·2%)	—	—
Yes	60	11 (18·3%)	2·2	1·2–4·0
ST segment elevation:				
No	306	28 (9·2%)	—	—
Yes	168	17 (10·1%)	1·1	0·6–1·9
Extrasystoles:				
No	455	43 (9·5%)	—	—
Yes	19	2 (10·5%)	1·1	0·3–3·5
PTF:				
< 10 mm ms	190	14 (7·4%)	—	—
10–20 mm ms	131	12 (9·2%)	1·2	0·6–2·6
> 20 mm ms	153	19 (12·4%)	1·7	0·9–3·2
QTc				
< 400 ms	147	12 (8·2%)	—	—
400–440 ms	182	13 (7·1%)	0·9	0·4–1·8
> 440 ms	145	20 (13·8%)	1·7	0·9–3·3
		Other clinical variables		
Age:				
< 50 yr	116	11 (9·5%)	—	—
50–60 yr	165	11 (6·7%)	0·7	0·3–1·5
> 60 yr	193	23 (11·9%)	1·3	0·6–2·5
Sex:				
Female	102	12 (11·8%)	—	—
Male	372	33 (8·9%)	0·7	0·4–1·4
Previous AMI:				
No	331	21 (6·3%)	—	—
Yes	143	24 (16·8%)	2·6	1·5–4·6
Previous angina:				
No	301	23 (7·6%)	—	—
Yes	173	22 (12·7%)	1·7	1·0–2·9
Peak CK:				
< 300 IU/l	194	14 (7·2%)	—	—
300–600 IU/l	121	16 (13·2%)	1·8	0·9–3·6
> 600 IU/l	159	15 (9·4%)	1·3	0·7–2·6
Killip class:				
I–II	439	36 (8·2%)	—	—
III–IV	35	9 (25·7%)	3·1	1·6–5·7
Early post-AMI angina:				
No	351	32 (9·1%)	—	—
Yes	123	13 (10·6%)	1·2	0·6–2·1
Late VF or VT:				
No	460	40 (8·7%)	—	—
Yes	14	5 (35·7%)	4·1	1·8–7·8
Late SVT or AF				
No	452	40 (8·8%)	—	—
Yes	22	5 (22·7%)	2·6	1·1–5·3
Late heart failure				
No	411	27 (6·6%)	—	—
Yes	63	18 (28·6%)	4·3	2·5–7·3
Heart rate at discharge:				
< 65 beats/min	185	12 (6·5%)	—	—
65–75 beats/min	144	12 (8·3%)	1·3	0·6–2·7
> 75 beats/min	145	21 (14·5%)	2·2	1·2–4·3
Predischarge CTR > 50%				
No	379	24 (6·3%)	—	—
Yes	95	21 (22·1%)	3·5	2·0–5·9
Pulmonary congestion				
No	445	39 (8·8%)	—	—
Yes	29	6 (20·7%)	2·4	1·1–4·7
Medication at discharge:				
Digitalis				
No	383	24 (6·3%)	—	—
Yes	91	21 (23·1%)	3·7	2·1–6·2

	No	*Mortality*	*Risk ratio*	*95% confidence interval*
Diuretics.				
No	312	19 (6·1%)	—	—
Yes	162	26 (16·0%)	2·6	1·5–4·6
β blockers:				
No	205	24 (11·7%)	—	—
Yes	269	21 (7·8%)	0·7	0·4–1·2
Antiarrhythmics.				
No	459	40 (8·7%)	—	—
Yes	15	5 (33·3%)	3·8	1·7–7·4
Anticoagulants:				
No	384	32 (8·3%)	—	—
Yes	90	13 (14·4%)	1·7	0·9–3·1

PTF, P terminal force in V1; AMI, acute myocardial infarction; CK, serum creatine kinase; VF, ventricular fibrillation, VT, sustained ventricular tachycardia, SVT, paroxysmal supraventricular tachycardia; AF, paroxysmal atrial fibrillation or atrial flutter; CTR, cardiothoracic ratio.

have a value of 1 if the property considered is present and 0 if it is not. Continuous variables were divided into thirds and indicator variables for the middle and high risk categories were considered for inclusion in the model. The BMDP package was used; this selects, in a stepwise fashion, predictor variables based on the maximum likelihood ratio. This provides a measure of significance and has an asymptotic χ^2 distribution. Thus variables were included in the model if their inclusion substantially improved the log likelihood ($p < 0{\cdot}10$) or if their removal led to a substantial decrease ($p < 0{\cdot}15$). Forward selection and backward elimination of the variables yielded the same models. Two models were developed; the first was based on the 12 lead electrocardiogram variables alone, and the other on the clinical variables alone.

The regression coefficients of each model have a direct epidemiological implication: each coefficient represents the log odds of dying when other variables in the model are controlled. Its antilogarithm is the relative risk of the event considered. As an example, if the regression coefficient for previous myocardial infarction is 1, its antilogarithm (e^1) is 2·7. This means that the risk of dying within one year for patients with a previous infarction is 2·7 times as high as it is for patients who had no previous myocardial infarction. The coefficients are related to the relative odds. They are a good approximation for the relative risk because mortality is rare (45 out of 474 died, 9·5%).

Results

PREDICTION OF MORTALITY BY UNIVARIATE ANALYSIS

Table 3 gives the results of univariate analysis of the percentage mortality. Of the 12 lead electrocardiographic variables, QRS score and ST depression gave statistically significant risk ratios, while QTc and P terminal force in V1 were less predictive. Of the clinical variables, previous myocardial infarction, preinfarction angina, Killip class III or IV, late paroxysmal atrial tachycardia or fibrillation, late heart failure, heart rate > 75 beats/minute, cardiothoracic ratio > 50%, and pulmonary congestion on *x* ray were all associated with significant risk ratios. Of the drugs being taken at discharge, three reached significance—digitalis, diuretics, and antiarrhythmics.

PREDICTION OF MORTALITY BY MULTIVARIATE ANALYSIS

Table 4 (upper part) shows the results of stepwise logistic regression of one year mortality on variables in the 12 lead electrocardiogram. QRS score >5, presence of ST depression, and QTc > 440 ms were found to be of predictive value. In particular, the presence of a QRS score >5 or of QTc > 440 ms was associated with a 1·8 fold increase in the patient's risk of dying within one year, and the presence of ST depression multiplied the risk by 2·2.

Table 4 (lower part) summarises the logistic regression results for the clinical variables. The presence of previous myocardial infarction, late heart failure, indication for digitalis at discharge or a cardiothoracic ratio >50%, and an indication for antiarrhythmic drugs were all independently of predictive value. As there are three variables related to pump failure: clinical signs of late heart failure, use of digitalis, and cardiothoracic ratio >50%, the construction of the model cannot be straightforward. The regression model assumes multiplicativity of the different factors. That is, if two factors are present, each with a relative risk of 3, then the combined relative risk will be $3 \times 3 = 9$. As the three variables above to a large extent measure the same phenomenon, the assumption of multiplicity must

Table 4 *Variables eventually retained in the logistic function of the risk of dying within one year*

	*No**	*Coefficient*	*SE*	*Relative risk*	*Log likelihood*
12 lead ECG·					
QRS score > 5	190	0·6	0·3	1·8	−142·2
ST segment depression	60	0·8	0·4	2·2	
QTc > 440 ms	145	0·6	0·3	1·8	
Constant	474	−2·9	0·3	—	
Clinical variables:					
Previous AMI	143	1·1	0·3	3·0	−122·7
Late heart failure	63	1·1	0·4	3·0	
Digitalis or CTR > 50%	148	1·4	0·4	4·1	
Antiarrhythmics	15	1·4	0·6	4·1	
Constant	474	−3·7	0·3	—	

*Number of patients in whom the property considered was present.
AMI, acute myocardial infarction, CTR, cardiothoracic ratio

be questioned. We investigated this by using interaction terms in our model. We concluded that digitalis and a cardiothoracic ratio >50% can be combined. As a consequence, the relative risk of a patient with a cardiothoracic ratio of >50% who also uses digitalis remains 4·1. If clinical signs of late heart failure are present, however, the relative risk increases to 12·1. This is also the case if the late heart failure is present with either a cardiothoracic ratio of >50% or digitalis treatment.

The addition of the variables of the 12 lead electrocardiogram to the model already containing the other clinical variables gave only a marginally better fit for the data; the improvement of the log likelihood was 0·32 ($\chi^2 = 0{\cdot}64$, $p > 0{\cdot}60$). From this we concluded that the variables of the 12 lead electrocardiogram do not make an independent contribution to the prediction of one year mortality that is additional to that of the other clinical variables alone. Nevertheless, if clinical data are not available, the 12 lead electrocardiogram can, to a certain extent, replace them. The mean predicted probability of dying for patients who actually died is 0·12 based on the electrocardiographic model and 0·23 based on the clinical model. This demonstrates the greater ability of the clinical variables to identify patients who will die prematurely. The mean predicted probability of surviving for patients who actually survived is 0·91 based on the electrocardiographic models and 0·92 based on the clinical model, demonstrating that survival can equally well be predicted by the electrocardiographic or clinical variables.

Discussion

There is a considerable overlap between information derived from non-invasive and invasive tests when assessing the prognosis of patients after myocardial infarction. The most efficient strategy, with the highest ratio of information to cost and risk, in an individual patient is not obvious.

We have compared the prognostic value of tests that are not always performed at discharge, such as exercise testing, radionuclide ventriculography, and the 24-hour ambulatory electrocardiogram with that of other clinical variables.[1]

In this study we assessed the prognostic value of the predischarge 12 lead electrocardiogram, which is routine and not expensive, to establish whether it provides information that is additional to the known clinical information and tests.

We believe that our study is the first in which a consecutive series of patients admitted to one coronary care unit was sufficiently large to allow a multivariate analysis based on predischarge clinical and electrocardiographic variables; in which patients at relatively low risk were studied (those with conduction defects, ventricular hypertrophy and atrial fibrillation were excluded); and which included, among other electrocardiographic variables, Selvester's QRS score[8] which in the past few years has been increasingly used to assess the extent of myocardial damage and the prognosis. In other studies, however, its prognostic value was not compared by multivariate analysis with that of other electrocardiographic or clinical variables. A large study by the Coronary Drug Project Research Group also determined the relative prognostic value of clinical and electrocardiographic variables in patients after infarction.[2] The conclusion of that study of 2035 patients followed for three years was that ST depression ⩾1 mm of the "ischaemic" type was the most important independent risk predictor of all the clinical and electrocardiographic findings studied, including Q waves, ventricular conduction defects, atrial fibrillation, and extrasystoles.

We confirmed that many electrocardiographic variables are predictive of survival (tables 3 and 4). The highest risk ratios for mortality (2·2) were obtained for ST segment depression. These figures accord with those reported in the Coronary Drug Project Research study.[2] We, however, did not confirm the predictive value of extrasystoles and of ST elevation. This difference may be attributable to the different populations in the two studies. Patients entered the Coronary Drug Project Research study later (at least three months after the most recent infarction) and patients with ventricular conduction defects and atrial fibrillation were included. Patients were followed for longer, up to three years, in the Coronary Drug Project Research study. We studied a consecutive series of patients evaluated at hospital discharge who did not have conduction abnormalities or atrial fibrillation; follow up lasted for a year. For hospital survivors of myocardial infarction the mortality is highest in the first three to six months.[1] Unlike the present study early deaths were excluded from the Coronary Drug Project Research study.

In table 2 some predischarge variables of the 474 patients in the study group are compared with those of patients excluded from the study because of ventricular conduction defects, hypertrophy, or atrial fibrillation. These data clearly indicate that patients with normal QRS pattern had much less extensive myocardial damage. This is consistent with their lower mortality during follow up. The electrocardiogram is therefore helpful in distinguishing patients without signs of conduction disturbances, ventricular hypertrophy, or atrial fibrillation—a relatively low risk group—from those in whom at least one of the above conditions is present and in whom the risk of premature death is much higher.

The QRS score and, to a lesser extent, P terminal force in V1 and QTc were also predictive of mortality (table 3). QRS score is directly related to the extent of myocardial damage[8] and it has been shown to correlate fairly well with left ventricular ejection fraction. In the present series the coefficient of correlation between radionuclide ejection fraction and QRS score was −0·53 (SEE 11%) in 417 patients. The coefficient was similar (r = −0·57, SEE 11%) when the analysis was limited to 296 patients with a first myocardial infarction.

Others have shown that the P terminal force measured from precordial lead V1 correlates with left atrial overload.[9] Siltanen *et al* reported that the P terminal force was the strongest independent predictor of mortality derived from predischarge electrocardiogram in 457 post-infarction patients.[7] ST segment abnormalities were the second. These workers, however, did not measure the Selvester QRS score. Their population was also different and they did not exclude patients with ventricular conduction abnormalities or ventricular hypertrophy. In our study these patients had a greater P terminal force in V1. This indicates more severe left ventricular dysfunction (table 2); and there was a corresponding increase in clinical signs of heart failure and a lower ejection fraction in these patients (table 2).

Mortality was higher in patients with prolonged QTc: in a seven year follow up of 55 patients with a recent infarction Schwartz and Wolf found that a prolonged QTc (>440 ms) measured during serial electrocardiographic measurements increased the risk of sudden death by a factor of 2 1.[4] More recently, Ahnve *et al* confirmed that a prolonged QTc is predictive of premature death in patients after infarction.[5] When they used a cut-off of 440 ms they found that QTc gave a sensitivity of 77% and a specificity of 84%. They limited the study to patients not on medical treatment, which might influence the QTc interval.

In contrast with QRS score and P terminal force in V1, which are related to pathophysiological phenomena such as the extent of myocardial damage and left atrium overload, the findings for ST depression and QTc interval are difficult to interpret. Both were predictive of mortality in our study, in which the clinically prescribed medication was not discontinued. Medication is known to be one of the many factors that affects both variables.[5]

In multivariate analysis ST segment depression, QTc, and QRS score were the independent predictors of mortality (table 4). Of the clinical features the most useful independent prognostic variables were persistent heart failure, a history of previous myocardial infarction, cardiomegaly on the chest *x* ray, and the use of digitalis and antiarrhythmics at discharge. These variables all relate directly or indirectly to poor ventricular function. Several clinical and electrocardiographic variables provided useful prognostic information. When multivariate analysis was applied to the combination of clinical and electrocardiographic variables, however, the inclusion of electrocardiographic variables did not improve the prognostic information derived from the clinical data.

We conclude that the predischarge electrocardiogram can provide important prognostic information about post-infarction patients without intraventricular conduction abnormalities, ventricular hypertrophy, or atrial fibrillation, in whom clinically prescribed medication has not been discontinued, and that persistent ST segment depression, the Selvester QRS score,[8] and QTc are independent predictors of survival. These electrocardiographic variables alone are not sufficiently powerful to improve risk assessment when added to other clinical information routinely collected in hospital.

References

1 Fioretti P, Brower RW, Simoons ML, *et al.* The relative value of clinical variables, bicycle ergometry, resting radionuclide ventriculography and 24-hour ambulatory electrocardiographic monitoring at discharge to predict one year survival after myocardial infarction. *J Am Coll Cardiol* 1986;**8**:40–9.

2 Coronary Drug Project Research Group. The prognostic importance of the electrocardiogram after myocardial infarction. *Ann Intern Med* 1972;77:677–89.

3 Coronary Drug Project Research Group. Prognostic importance of premature beats following myocardial infarction. *JAMA* 1973;**233**:1116–24.

4 Schwartz PJ, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978;57:1074–7.

5 Ahnve S, Gilpin E, Madsen EB, *et al.* Prognostic importance of QT interval at discharge after acute myocardial infarction: a multicenter study of 865 patients. *Am Heart J* 1984;**108**:395–400.

6 Fioretti P, Brower RW, Lazzeroni E, *et al.* Limitations of a QRS scoring system to assess left ventricular function and prognosis at hospital discharge after myocardial infarction. *Br Heart J* 1985;**53**:248–52.

7 Siltanen P, Pohjola-Sintanen S, Haapakoski J, *et al.* The mortality predictive power of discharge electrocardiogram after first acute myocardial infarction. *Am Heart J* 1985;**109**:1231–7.

8 Hindman NB, Schocken DD, Widman M, *et al.* Evaluation of a QRS scoring system for estimating myocardial infarct size. V. Specificity and method application of the complete system. *Am J Cardiol* 1985;55:1485–90.

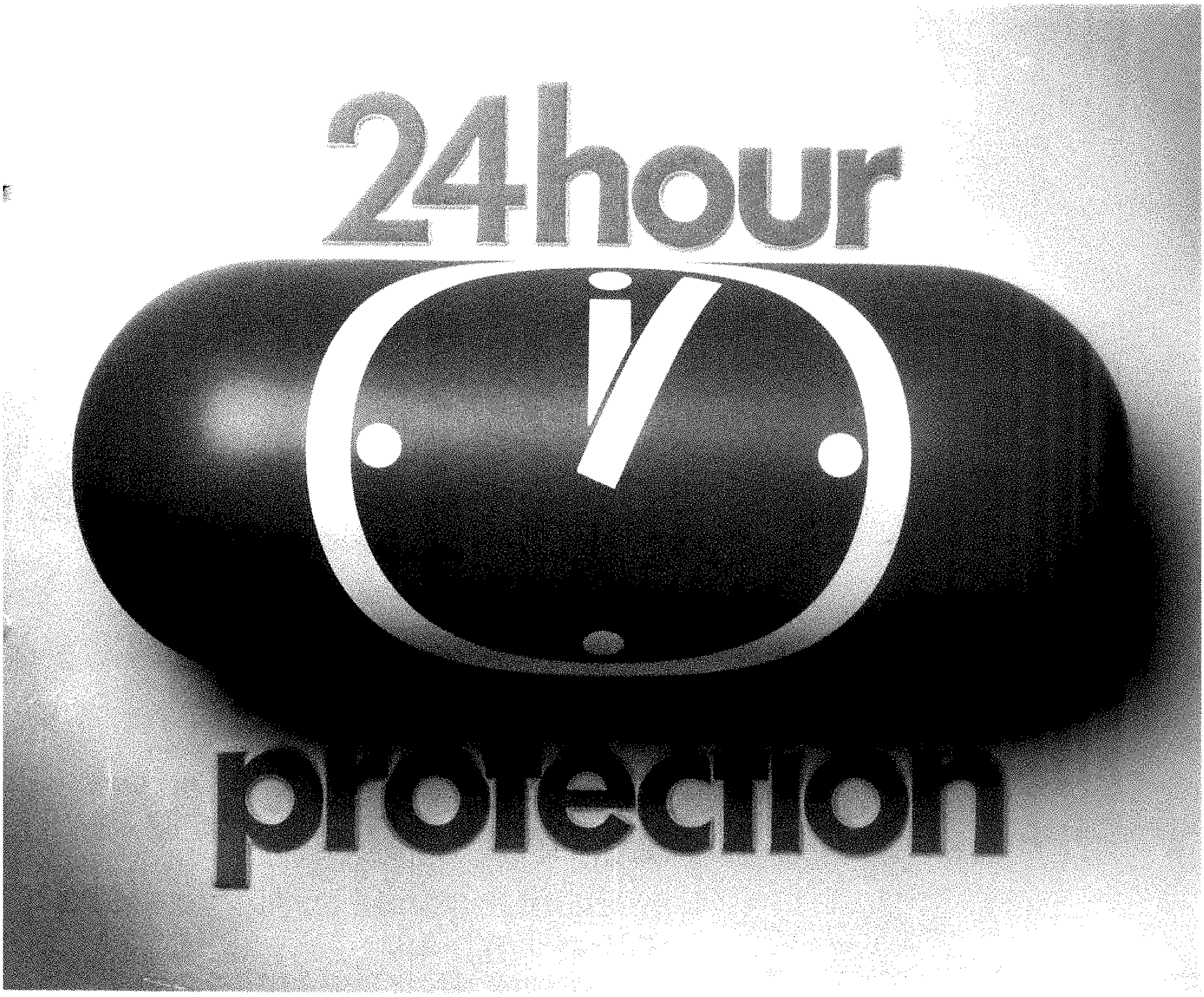
9 Heikkila J, Hugenholtz PG, Tabakin BS. Prediction of left heart filling pressure and its sequential change in acute myocardial infarction from the terminal force of the P wave. *Br Heart J* 1973;**35**:142–51.

10 Williams WL, Nair RC, Higginson LAJ, *et al.* Comparison of clinical and treadmill variables for the prediction of outcome after myocardial infarction. *J Am Coll Cardiol* 1984;4:477–86.

11 Simoons ML, Serruys PW, van den Brand M, *et al.* Improved survival after early thrombolysis in acute myocardial infarction. *Lancet* 1985;**ii**:578–82.

12 Serruys PW, Simoons ML, Suryapranata H, *et al.* Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 1986;7:729–42.

13 Simoons ML, Serruys PW, van den Brand M, *et al.* Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. *J Am Coll Cardiol* 1986;7:717–28.



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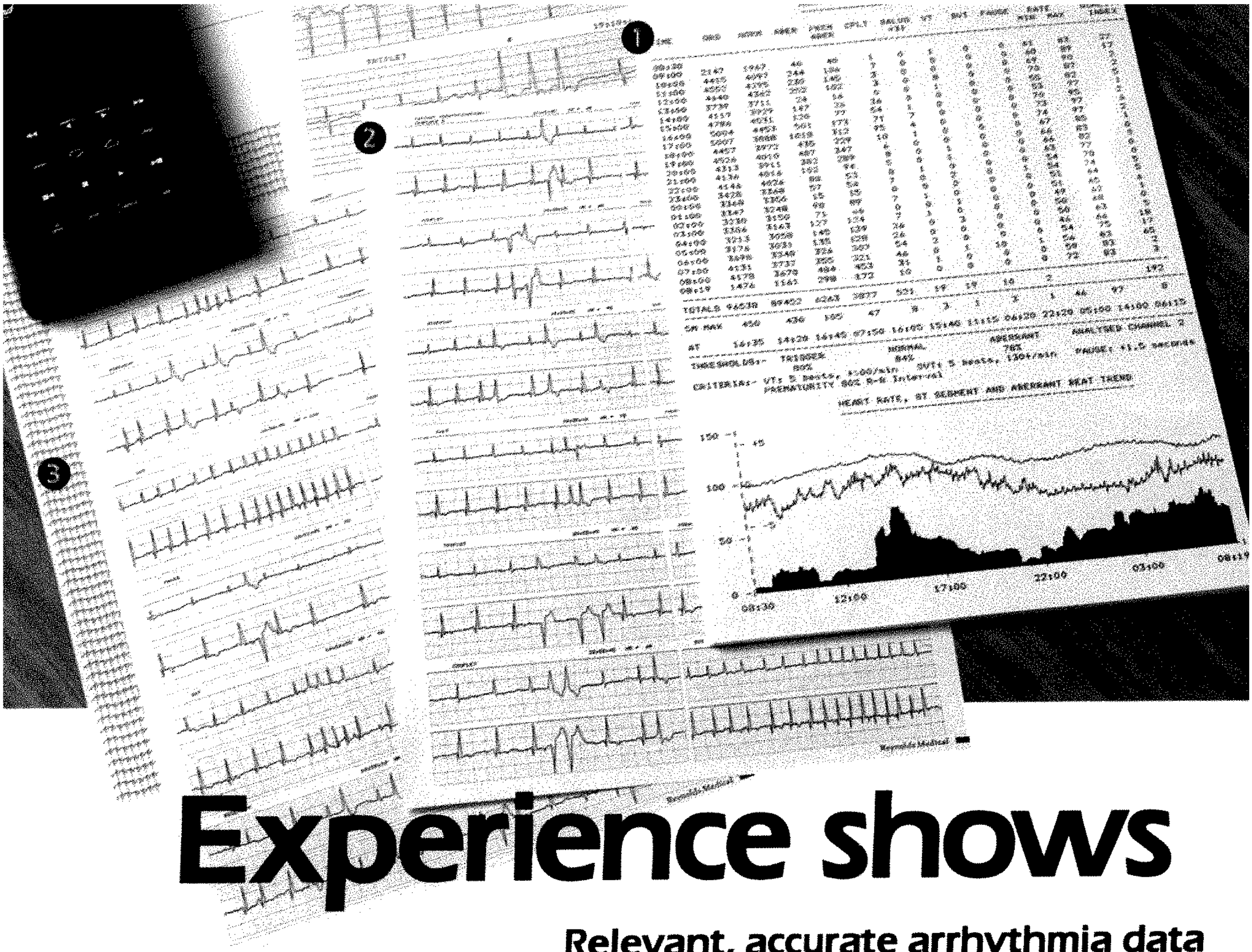

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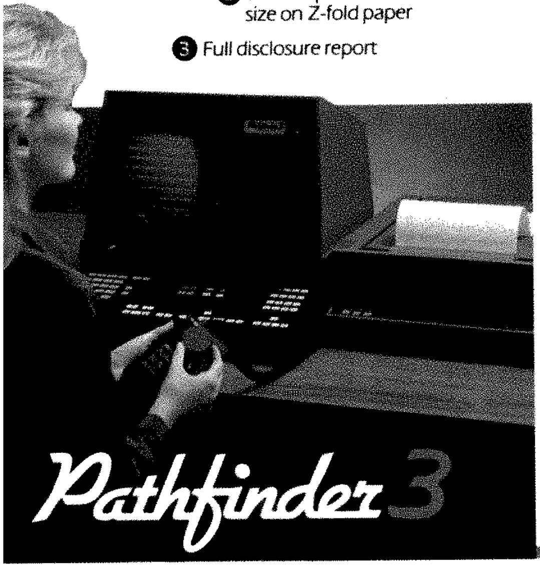

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Prognostic stratification of patients after myocardial infarction

DONAL P MURRAY, MAHMOOD SALIH, LIP BUN TAN,
R GORDON MURRAY, WILLIAM A LITTLER

From the Department of Cardiovascular Medicine, University of Birmingham, East Birmingham Hospital, Birmingham

SUMMARY An attempt was made to stratify risk of subsequent cardiac events in post-infarct patients according to a combination of the results of clinical assessment, routine diagnostic investigations, and pre-discharge exercise testing in 350 consecutive patients who were followed up for one year. Patients were classified prospectively on the basis of the extent of myocardial damage as assessed by peak enzyme release, reciprocal change on the electrocardiogram at the time of myocardial infarction, Norris prognostic index, ability to perform a pre-discharge exercise test (and test result), and ability to tolerate β adrenergic blockade on discharge. Of the 50 patients with contraindications to pre-discharge exercise testing, 26% died or had reinfarctions compared with 9% of the 300 exercised patients; the 24 non-exercised patients with evidence of extensive myocardial damage or reciprocal changes on the electrocardiogram were particularly at risk. Similarly, among the 300 exercised patients, extensive myocardial damage, reciprocal change on the electrocardiogram, and ST depression on exercise testing were the major risk markers in that each identified at least 75% of the patients who had subsequent cardiac events. The 63 exercised patients who had all three of these major risk markers constituted a high risk group: 18 (29%) died or had reinfarction. Of the remaining 237 patients, only 9 (4%) had cardiac events. The 35 high risk patients with exercise induced angina pectoris or clinical contraindications to β blockade were particularly at risk; 15 (43%) died or had reinfarction.

This approach to risk stratification identified a small cohort of high risk patients in a large population of myocardial infarction survivors; it also identified a large group with a very low risk of subsequent cardiac events.

The prognosis after recovery from acute myocardial infarction is chiefly related to two factors; namely the degree of damage to the left ventricle at the time of infarction and the amount of myocardium still at risk because it is supplied by critically diseased coronary arteries.[1–3] It is not surprising, therefore, that an array of historical, clinical, and exercise variables have been identified as markers of increased risk for the post-infarct patient.[4–6] All of these risk factors when used in isolation lack specificity—they all produce a large proportion of false positive results.[7 8]

The aim of this study was, therefore, to stratify our post-infarct population into risk categories by combining the results of clinical assessment of the patient, routine diagnostic investigations, and pre-discharge exercise testing.

Patients and methods

STUDY POPULATION

Over an 18 month period we studied all patients aged less than 66 years who survived to discharge from our coronary care unit. Those with electrocardiographic and enzymatic evidence of myocardial infarction were enrolled in the study.[9] There were 350 patients who fulfilled the entry criteria. The mean (SD) age of the study population was 53 (3) years and the male:female ratio was 4·9:1. Of the 350 patients, 50 did not perform a pre-discharge exercise test: 38 because of heart failure, seven because of other serious medical conditions, three for logistical reasons, and two refused to exercise.

Requests for reprints to Dr Donal P Murray, Department of Medicine, Cork Regional Hospital, Wilton, Cork, Ireland

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FOLLOW UP

All patients were regularly followed up in our cardiology clinic. The mean duration of follow up was 13 months, and all patients were followed for at least six months. During the follow up period 23 patients died, 34 had a further myocardial infarction, and 40 patients had one or other of these cardiac events. All the deaths were cardiac, occurring either suddenly at home or in association with a recurrent infarction.

DRUG TREATMENT

At the time of exercise 62 patients were taking a β adrenergic blocker, and after discharge all patients were prescribed metoprolol (100 mg twice a day) for secondary prevention unless this treatment was clinically contraindicated. In total, 90 patients were not given a β blocker: 60 because of heart failure, 14 because of peripheral vascular disease, four because of heart block, and 12 because of other serious medical conditions.

VARIABLES STUDIED

During the in-hospital period the following variables were recorded on all patients: Norris prognostic index; reciprocal changes on the electrocardiogram; the degree of left ventricular damage; the results of a pre-discharge exercise test; the prescription of a β adrenergic blocker on discharge.

Norris prognostic index

Each patient's Norris prognostic index was computed by giving a weighted score for age, history of ischaemia, radiological heart size, and evidence of cardiac failure on the day of admission. Norris *et al* have previously demonstrated increasing mortality with increasing index.[4] Patients were subdivided by median Norris index into groups with high and low values.

Reciprocal changes

Myocardial infarct regions were defined as follows: in anterior infarction changes were seen in leads V1–V5; in inferior infarction in leads II, III, and aVF; and lateral infarction was defined as changes in leads I, aVL, and V6. Reciprocal changes were defined as the presence of >0·1 mV of horizontal or downsloping ST depression which extended for 80 ms beyond the J point of the electrocardiogram in leads remote from the site of infarction.

Myocardial damage

Extensive myocardial damage was defined as a peak enzyme release in excess of five times the upper limit of normal for our laboratory—that is a peak serum aspartate transaminase > 200 IU or a peak lactate dehydrogenase > 2000 IU. In the absence of either of these findings, a history of previous myocardial infarction was also taken to indicate severe left ventricular damage.

Exercise test

Treadmill exercise testing was carried out on the day of discharge from hospital according to a modified Naughton's protocol.[10] Exercise was stopped at 18 minutes (7 metabolic equivalents of energy expenditure at rest) or earlier if the patient developed limiting symptoms, significant ventricular arrhythmias, > 0·4 mV of ST depression, or a fall in systolic blood pressure of 20 mm Hg or more from the previous peak systolic value.

Tests were classified as positive if there was more than 0·1 mV of horizontal or downsloping ST segment depression which extended for 80 ms beyond the J point of the electrocardiogram or if the patient had an abnormal blood pressure response to exercise—that is, failure of the systolic blood pressure to rise from the resting value or a fall in the systolic blood pressure of 10 mm Hg or more from the previous peak systolic value.

In addition, the presence or absence of exercise induced angina pectoris was noted in all patients. In view of the lack of objectivity of this symptom, however, it was not used to classify tests as positive or negative.

β blocker prescription

As cardiac failure was the most common contraindication to β blockade in our population, it seemed likely that patients who were not taking β blockers would constitute a high risk group. Presence or absence of β blockade on discharge was, therefore, noted in all patients.

STATISTICAL ANALYSIS

Student's *t* test was used to assess differences between means of independent observations. The χ^2 test was used to assess differences between proportions. In the text and tables mean (SD) values are given.

Results

Table 1 demonstrates the ability of each of the risk markers to identify those patients who died or had a reinfarction. The median Norris index of the total population of 350 patients was 4·81. There was no difference in the frequency of subsequent cardiac events when the patients were subdivided on the basis of the median index. Similarly, stratification of the patients into centiles on the basis of the Norris index failed to identify cohorts that were at

Table 1 *Ability of the risk markers to identify from the total population of 350 patients those who died or had a reinfarction (RI)*

Marker	*Risk marker positive*		*Risk marker negative*		*p*
	Total	*Death/RI (%)*	*Total*	*Death/RI (%)*	
Norris index > median	175	21 (12)	175	19 (11)	NS
Reciprocal change	204	33 (33)	146	7 (5)	**
Extensive myocardial damage	171	31 (18)	179	9 (5)	***
No exercise test	50	13 (26)	300	27 (9)	***
No β blocker	90	23 (26)	260	17 (7)	***

**p < 0·01, ***p < 0·001.

Table 2 *Ability of the risk markers to identify from among the 300 exercised patients those who died or had a reinfarction (RI)*

Marker	*Risk marker positive*		*Risk marker negative*		*p*
	Total	*Death/RI (%)*	*Total*	*Death/RI (%)*	
Norris index > median	150	12 (8)	150	15 (10)	NS
Reciprocal change	172	23 (13)	128	4 (3)	**
Extensive myocardial damage	135	21 (16)	165	6 (4)	***
Positive exercise test	170	23 (14)	130	4 (2)	**
Exercise induced angina	78	16 (21)	195	11 (6)	**
No β blocker	42	11 (26)	258	16 (6)	***

**p < 0·01; ***p < 0·001

increased risk. Patients with reciprocal changes at the time of infarction had a higher frequency of death and re-infarction than the group without this finding (p < 0·01). Similarly, those with severe myocardial damage, those judged unfit to perform a pre-discharge exercise test, and those judged unlikely to tolerate long term β blockade were all at increased risk of death or reinfarction compared with patients who did not have these risk markers (p < 0·001).

One hundred and thirty four (70%) of the 172 patients with reciprocal changes also developed ST depression on exercise. Among the 300 exercised patients, those with reciprocal changes, extensive myocardial damage, a positive exercise test or exercise induced angina, and patients judged unlikely to tolerate a β blocker were all at increased risk of death and reinfarction (p < 0·01; table 2). Among the exercised patients, the presence of reciprocal changes, extensive myocardial damage, and positive exercise test were the most sensitive risk markers; each identified more than 20 of the 27 patients who died or had reinfarction. Sixty three of the exercised patients had all three of these risk markers—that is, reciprocal changes, extensive myocardial damage, and a positive exercise test result. Eighteen (67%) of the 27 patients who died or had reinfarction fell into this high risk group (p < 0·001; table 3).

Thirty five of the 63 high risk patients had exercise induced angina pectoris or were judged unlikely to tolerate long term β blockade (figure). This subgroup contained 15 of the 18 high risk patients who had complications. Only three (11%) of the 28 remaining high risk patients died or had reinfarction (p < 0·01; figure).

Among the 50 patients unable to perform a pre-discharge exercise test, 10 (42%) of the 24 with severe left ventricular damage and reciprocal changes had complications compared with three (12%) of the 26 without both of these markers (p < 0·05; figure). Only two of the 50 non-exercised patients were prescribed a β blocker on discharge.

Table 3 *Clinical outcome for the high and low risk patients*

Outcome	*High risk (n = 63)*	*Low risk (n = 237)*	*p*
Death (14)	11 (17%)	3 (1%)	***
RI (24)	17 (27%)	7 (3%)	***
Death or RI (27)	18 (29%)	9 (4%)	***

High risk = positive exercise test, reciprocal changes on the electrocardiogram, and extensive myocardial damage.
Low risk = patients who did not have all three major risk markers.
***p < 0·001 RI, reinfarction

Discussion

Our results demonstrate that by combining the results of clinical assessment, routine diagnostic investigations, and pre-discharge exercise testing we could identify with a high degree of accuracy those infarct survivors who were at high risk of death and reinfarction during the next year. Most of our patients constituted a low risk group and had a good prognosis. Reciprocal changes on the electrocardiogram at the time of infarction, evidence of

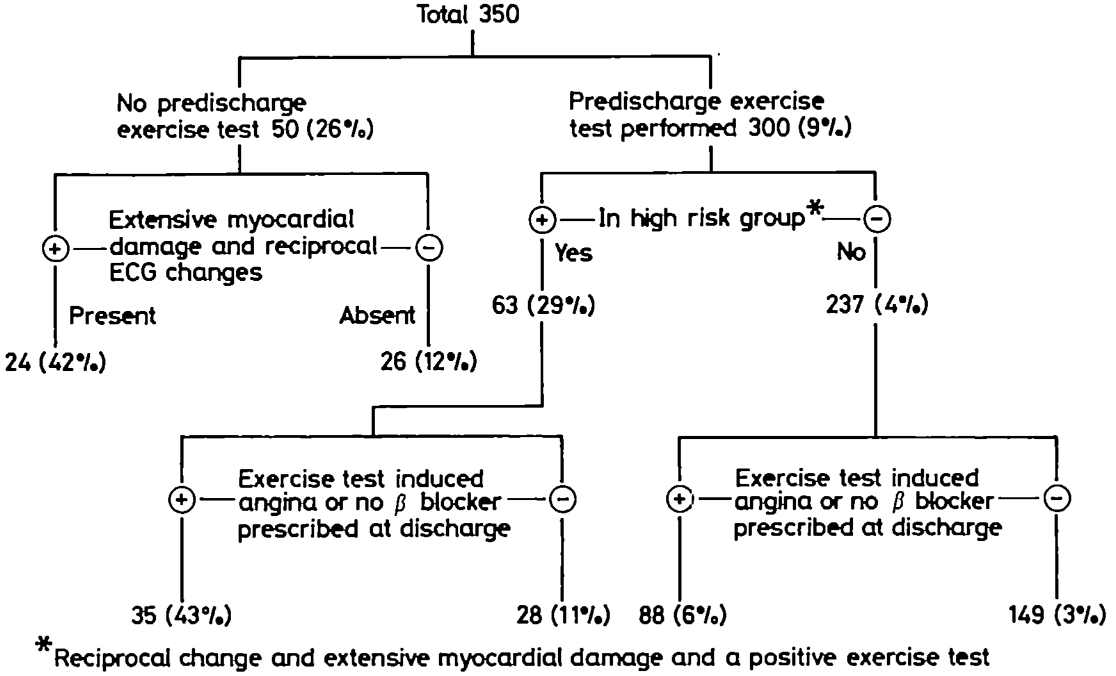
Total 350
No predischarge exercise test 50 (26%)
Predischarge exercise test performed 300 (9%)
Extensive myocardial damage and reciprocal ECG changes
Present
Absent
24 (42%)
26 (12%)
In high risk group*
Yes
No
63 (29%)
237 (4%)
Exercise test induced angina or no β blocker prescribed at discharge
Exercise test induced angina or no β blocker prescribed at discharge
35 (43%)
28 (11%)
88 (6%)
149 (3%)
*Reciprocal change and extensive myocardial damage and a positive exercise test

Figure *Subdivision of patients according to clinical and exercise test results. The figures in parentheses are percentages of each group who died or had a reinfarction.*

severe myocardial damage, inability to perform a pre-discharge exercise test or to tolerate β blockade, and a positive exercise test or exercise induced angina pectoris were all significantly associated with a poor prognosis.

When individual risk markers are used in post-infarct patients they lack specificity. This lack of specificity is evident from our results and those of other investigators. Geltman *et al* and Sobel *et al* demonstrated that patients with large infarcts, as assessed by peak enzyme release, had a worse long term prognosis than patients with a small peak enzyme release.[1 11] None the less, 70% of their patients with large infarcts survived more than four years. Similarly, 82% of our patients with evidence of severe myocardial damage had no complications during our one year follow up.

Hlatky *et al* reported an 80% five year survival rate in their patients with reciprocal changes on the electrocardiogram at the time of infarction compared with 92% in those patients without such changes.[8] Similar results were reported by Geltman *et al.*[1] These results are again consistent with ours: although we found reciprocal change to be a significant marker of increased risk 84% of our patients with this finding had no complications.

Many workers have noted that patients considered to be medically ineligible for pre-discharge exercise testing have a bad prognosis.[5 7 12] Our non-exercised patients were also at increased risk, yet only 26% had complications. In the papers that have demonstrated increased risk in patients with positive pre-discharge exercise tests, the frequency of complications was still relatively low: DeBusk *et al* (9·7%),[5] Sami *et al* (22%),[13] and Theroux *et al* (27%).[6] These results are consistent with our figure of 14%. Similarly, despite the value of exercise induced angina pectoris as a risk marker, 74% of the Montreal patients[6] and 79% of our patients with this finding had no complications during the one year follow up.

In the Norwegian multicentre study of timolol after acute myocardial infarction 40% of those excluded from the study because of medical contraindications died during the next six months.[14] This figure is comparable with the 26% incidence of complications in our patients who were not treated with β blockers.

It is clear, therefore, that, in keeping with other investigators, we were able to identify several statistically significant risk markers in a post-infarct population. When used individually these risk markers lacked specificity. Combining them enabled us to identify with a greater degree of accuracy those patients who were at risk of death or reinfarction. In the group of 50 patients considered to be medically ineligible for exercise testing 10 of the 13 who developed complications were included in the subgroup of 24 who also had reciprocal changes and severe left ventricular damage. No study had previously attempted to further stratify, on a prognostic basis, patients judged ineligible for pre-discharge exercise testing. The prognostic implications of a positive exercise test were greatly increased by the presence of reciprocal changes and severe left ventricular damage. Conversely, only 4% of the 237 patients who did not have all three major risk factors had complications ($p < 0{\cdot}001$). Although exercise induced angina pectoris and inability to tolerate long term β blockade were significant markers of increased risk, when they were used individually they identified only a small proportion of those patients who died or had a reinfarction. In combination they facilitated further prognostic stratification of the high risk patients. DeBusk *et al* had previously identified high risk groups in a post-infarct population on the basis of past history, ineligibility for pre-discharge exercise testing, and exercise test results.[5] In that study, however, none of the patients identified clinically as being at risk performed an exercise test, so the ability of a combination of risk factors to further enhance risk stratification was not clear. Krone *et al* also noted that inability to exercise carried a bad prognosis, whereas among their exercised patients the majority of deaths occurred in the group with a history of pulmonary congestion on the chest *x* ray, particularly when this was associated with an inadequate blood pressure response or poor exercise ability.[7]

In our population the Norris index alone was an insensitive marker of subsequent risk, regardless of the exercise test result. This is consistent with the findings of Krone *et al* who noted that age and past history, both components of the Norris index, were of little added value as risk markers in patients with positive exercise tests after myocardial infarction.[7] Norris *et al* found age to be an important prognostic marker.[4] They had no upper age limit for inclusion in their study, however, and a high proportion of the patients were older than 66, the upper limit for inclusion in the current study.

CLINICAL IMPLICATIONS

In a large population of infarct survivors, we have demonstrated that by integrating the results of clinical evaluation of the patient, routine diagnostic investigations, and pre-discharge exercise testing we could identify 67% with a very low incidence of subsequent cardiac events. In keeping with the results of Krone *et al* and the Coronary Artery Surgery Study,[7 15] this group of patients would be extremely unlikely to benefit from further investigations. Patients who were unable to perform a pre-discharge exercise test, particularly those with severe left ventricular damage and reciprocal changes on the electrocardiogram, had a poor prognosis—almost certainly due to gross left ventricular dysfunction. In the absence of evidence of reversible ischaemia, it seems unlikely that patients in this group would benefit from revascularisation. Dipyridamole-thallium-201 scintigraphy might possibly have a role in identifying a subgroup of non-exercised patients with reversible ischaemia who would benefit from grafting.[16] This hypothesis has not yet been examined. Finally, we were able to identify a small group of 63 patients with reciprocal changes and severe left ventricular damage who also had evidence of reversible ischaemia on exercise testing. This group contained 18 of the 27 exercised patients who died or had a reinfarction during the next year. The patients in this group with exercise induced angina pectoris or who were judged unlikely to tolerate β blockade were particularly at risk. It is possible that such patients might benefit from more rigorous medical treatment or even elective surgical treatment.[17]

References

1 Geltman EM, Ehsani AA, Campbell MK, *et al.* The influence of location and extent of myocardial infarction on long term ventricular dysrhythmia and mortality. *Circulation* 1979;**60**:805–14.

2 Taylor G, O'Neal J, Mellitts E. Prediction of clinical course, coronary anatomy and left ventricular function after recovery from an acute myocardial infarction. *Circulation* 1980;**9**:60–70.

3 De Feyter PJ, Eengie MJ, Dighton DH, Visser FC, De Jong A, Roos JP. Prognostic value of exercise testing, coronary angiography and left ventriculography, 6–8 weeks after myocardial infarction. *Circulation* 1982;**66**:527–36.

4 Norris RM, Caughey DE, Mercer CJ, Deeming LW, Scott PJ. Coronary prognostic index for predicting survival after recovery from acute myocardial infarction. *Lancet* 1970;**ii**:485–8.

5 DeBusk RF, Kraemer HC, Nash E. Stepwise risk stratification soon after acute myocardial infarction. *Am J Cardiol* 1983;**52**:1161–6.

6 Theroux P, Waters DD, Halphen C, Debaisieux JC, Mizgala HF. Prognostic value of exercise testing soon after myocardial infarction. *N Engl J Med* 1979;**301**:341–5.

7 Krone RJ, Gillespie JA, Weld FM, Miller JP, Moss AJ. Low-level exercise testing after myocardial infarction: usefulness in enhancing clinical risk stratification. *Circulation* 1985;**71**:80–9.

8 Hlatky MA, Califf RM, Lee KL, Pryor DB, Wagner GS, Rosati RA. Prognostic significance of precordial ST segment depression during inferior acute myocardial infarction. *Am J Cardiol* 1985;**55**:325–9.

9 Medias JE, Chahine RA, Goslin R, Blocklow DJ. A comparison of transmural and non-transmural acute myocardial infarction. *Circulation* 1974;**49**:498–507.

10 Naughton JP, Hellerstein HK. *Exercise testing and ex-*

Br Heart J 1987;57:319–28

How useful are the cold pressor test and sustained isometric handgrip exercise with radionuclide ventriculography in the evaluation of patients with coronary artery disease?

ROBIN J NORTHCOTE, MICHAEL B D COOKE*

*From the Department of Medical Cardiology, and *West of Scotland Health Boards, Department of Clinical Physics and Bio-Engineering, Victoria Infirmary, Glasgow*

SUMMARY The feasibility of using the cold pressor test and the sustained isometric handgrip test as alternatives to dynamic exercise for stressing the heart was investigated. Serial changes in heart rate, blood pressure, and left ventricular performance induced by these tests were studied by radionuclide ventriculography in patients with coronary artery disease and in normal volunteers. Both tests significantly increased heart rate and blood pressure. The reproducibility of serial evaluation of ejection fraction response to cold pressor and isometric handgrip stresses was satisfactory but the sensitivity for detecting coronary artery disease was not.

Both stress tests are valuable interventions for the serial evaluation of left ventricular function by radionuclide ventriculography, but they should not be used to detect coronary artery disease.

Stressing the heart may uncover latent abnormalities of myocardial contractility. For example, patients with stable angina pectoris may have normal ventricular function at rest but may develop abnormalities during stress. Several interventions have been used to stress the heart during examination by radionuclide ventriculography. These include increasing left ventricular afterload by administering drugs such as angiotensin[1 2] and phenylephrine[3] and the provocation of ischaemia by atrial pacing.[4 5]

Both the cold pressor test[6 7] and sustained isometric handgrip[8 9] are popular alternatives to dynamic exercise. Both tests eliminate movement artefact and can be applied to almost every patient. Dynamic exercise requires considerable cooperation from the patient and time to complete the tests; it is also more likely to precipitate symptoms in patients with ischaemic heart disease.

Several reports have examined the application of cold pressor test and sustained isometric handgrip exercise to the detection of coronary artery disease[6 10–12] but not the reproducibility of the responses when left ventricular function studies are used to determine serial changes in the same patient.

We have investigated the usefulness of both these interventions in the detection of coronary artery disease and their reproducibility in serial studies of left ventricular function.

Patients and methods

The protocol was approved by our local ethics committee and the Administration of Radioactive Substances Advisory Committee gave us permission to administer technetium-99m to three groups of subjects:

Group 1

Sixteen symptom free male volunteers were recruited from hospital staff and associates. All were in sinus rhythm; they were normotensive and lifelong non-smokers. They all had normal electrocardiograms at rest and during maximal graded exercise on a modified Bruce protocol.[13] The chest *x* ray and the cardiothoracic ratio were normal, and no subject was taking any medication at the time of the study. None had evidence of valvar or congenital heart disease, respiratory disease, or peripheral vascular disease and all were presumed to have normal hearts (table 1).

Requests for reprints to Dr Robin J Northcote, Department of Medical Cardiology, The Victoria Infirmary, Glasgow G42 9TY.

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Table 1 *Data on controls and subjects with coronary artery disease (CAD)*

	Group 1 *controls*	*Group 2* *CAD subjects**
Age (yr)	45 (7·0)	54 (8·1)
	(36–60)	(38–67)
Resting HR (beats/min)	63 (8·8)	67 (9·7)
Resting SBP (mm Hg)	119 (13·9)	135 (25·7)
Resting DBP (mm Hg)	69 (9·5)	80 (12·3)
Resting EF (%)	60·2 (11·4)	60·7 (8·3)

Results are expressed as mean (SD).
HR, heart rate, SBP, systolic blood pressure; DBP, diastolic blood pressure, EF, ejection fraction.
*Normal or nearly normal resting ejection fraction (50–79%)

Group 2

We also studied 20 male patients (mean age (SD) 54 (8) years) in whom a diagnosis of coronary artery disease and stable angina pectoris (New York Heart Association grade II or III) had been confirmed by a positive exercise electrocardiogram and also by evidence of coronary artery disease at coronary arteriography (n = 8) or by a documented history of myocardial infarction (n = 12). A stenosis of a major artery of >70% of the luminal diameter was regarded as significant coronary artery disease and a myocardial infarction was diagnosed on the basis of a prolonged episode of central chest pain, with characteristic electrocardiogram and cardiac enzyme changes, occurring at least one year before the study. These subjects had normal or nearly normal resting ejection fractions (range of 50–79%) (table 1). None had a history of or evidence of respiratory disease, valvar or congenital heart disease, unstable angina, cardiac arrhythmias or conduction abnormality, or cardiac failure. In the two weeks before the study they had taken only glyceryl trinitrate.

Group 3

To assess the variability of the resting ejection fraction and its response to the cold pressor test and sustained isometric handgrip exercise we studied 20 patients with chronic stable angina. Each underwent radionuclide ventriculography with a cold pressor test and sustained isometric handgrip exercise; ventriculography was repeated three times at intervals. After a baseline measurement, repeat studies were performed three and six months later. All were taking propranolol 80 mg three times a day and glyceryl trinitrate for chest pain. This treatment had been established for at least three months before these studies and remained unchanged.

STUDY PROTOCOL

Radionuclide ventriculography was performed at the same time of day in each subject. Red blood cells were labelled in vivo by giving an intravenous injection of technetium-99m (740 MBq (20 mCi)) into the right antecubital vein 20–30 minutes after 15 mg of stannous pyrophosphate had been given by the same route.[14] Radionuclide ventriculography was then performed in the left anterior oblique projection that gave the best separation of the right and left ventricles (usually 35–45°) and with a 10° caudal tilt. The same angle was used for each individual study interval. We used a Technicare Sigma 410 large field camera with a general all purpose low energy (140 KeV) parallel hole collimetor. Before each set of investigations the camera uniformity correction memory was calibrated with a technetium-99m flood field. An electrocardiographic signal from the patient obtained on an Elcomatic EM810 monitor was used to trigger the computer to record images synchronised with the R wave. Images in histogram mode in 16 sequential frames in a 64 × 64 data matrix with the zoom set at × 3 were stored in an ADAC (CGR) 7310 computer. Data collection stopped automatically after six minutes for resting studies and five minutes for stress studies. We used a framing rate of 16 frames per second for all studies. At the start of each study the computer calculated an average beat to beat interval from several cycles and then accepted image information from beats falling within a window (±20%) about the centre frequency. In the resting studies the centre frequency remained fixed throughout each study interval, thus excluding ectopic complexes. During stress studies the computer recalculated the mean beat to beat interval as the heart rate increased and thus retained the ability to reject ectopic complexes as it tracked steady changes in heart rate.

The composite 16 frame dynamic study was stored on disc for future analysis at the end of the study. Image analysis was performed by the Stanford Automatic left ventricular analysis program, which constructs an activity-time curve from which indices of left ventricular performance can be calculated.[15 16] Briefly, the edge detection algorithm is based on the application of a one dimensional La Placian filter to the end diastolic image vertically, horizontally, and along both diagonals. A search is made for the first edge which completely encloses the left ventricle, and the left ventricle is located by calculation of the x and y coordinates of the centre of gravity of an amplitude image constructed by the system. The program transforms the data to a frequency domain and retains the zero, first, second, and third harmonics as well as the diastolic image. A left ventricular region of interest is created and subsequently used for interpolative background subtraction. The region of interest is also used to create a 100 point volume curve from the frequency components. From this curve the system calculates the ejection fraction, and from its first derivative $\left(\frac{dVs}{dt} \text{ and } \frac{dVd}{dt}\right)$ it calculates the maximum rate of emptying and filling as end diastolic volumes per second in the control group.

To assess the reproducibility of the technique we performed two successive studies at rest. In all subjects the aquisition time was six minutes. An isometric handgrip test was followed by a cold pressor test. The right hand was used for both tests. There was an interval of at least 10 minutes between these studies, and blood pressure and heart rate had returned to basal values before the start of the cold pressor test. After the basal study at rest subjects performed a sustained isometric handgrip exercise with a hand dynamometer (Martin Vigorimeter). The patient's maximum voluntary contraction was determined and he was asked to maintain a handgrip at 30% of this value for five and half minutes; this allowed a lag period of 30 seconds before imaging started. Imaging was performed for five minutes in each subject.

The duration of the cold pressor test and time of the start of imaging have varied in previous studies. Some started 15–30 seconds after immersion of the hand in iced water with a 2–3 minute aquisition time.[7 10 17] Wainwright *et al* delayed the start of imaging for one minute and acquired images for five minutes.[6] We have found haemodynamic changes 15–30 seconds after immersion of the hand in ice, with maximal changes occurring between one and three minutes and being maintained for five minutes (unpublished observations). Because of these observations and because we were using a general purpose collimator we felt it appropriate to start imaging after 30 seconds and to acquire images for five minutes. In addition, this protocol allowed comparison with the almost identical protocol of Wainwright *et al.*[6]

For the cold pressor test the right hand was immersed to the level of the styloid process in a mixture of crushed ice and water. Throughout the test the water and ice round the hand were mixed to maintain the cold stimulus. Heart rate and blood pressure were monitored each minute before, during, and after both interventions by a Hitachi HME-20 pulse and blood pressure monitor.[18]

STATISTICAL ANALYSIS

Discrete variables were analysed by Student's paired *t* test and a Wilcoxon signed rank test was used for paired observations. Unpaired observations were analysed by Student's unpaired *t* test and a Mann-Whitney test. (The most conservative estimates of significance are reported.)

The variability of sequential ejection fraction measurements and the reproducibility in interventions were estimated by calculating the coefficient of variance. Values of ⩽10% were taken to indicate low variance and satisfactory reproducibility, values of 10–20% indicated moderate reproducibility, and values >20% unacceptable reproducibility. The 95% confidence interval about a resting ejection fraction was used to define a subsequent significant change during cold pressor test or sustained isometric handgrip exercise in the individual subject. This interval was calculated from pooled variance as described elsewhere.[19 20] Sensitivity (number of true positives divided by number of patients with coronary artery disease) and specificity (number of true negatives divided by number of patients without coronary artery disease) were calculated and expressed as percentages.

Results

Both the cold pressor test and sustained isometric handgrip exercise were tolerated well by all subjects. In each subject the tests were completed without the development of chest pain or electrocardiographic evidence of ischaemia. Several individuals complained of pain in the immersed hand during the cold pressor test which was most pronounced in the

Table 2 *Comparative mean heart rate (beats/min) and blood pressure (mm Hg) responses to sustained isometric handgrip stress in subjects with coronary artery disease (group 2, n = 20) and a normal control group (group 1, n = 16)*

	Time from start of isometric handgrip test (min)					
	Basal	*1*	*2*	*3*	*4*	*5*
CAD group:						
Heart rate	68 (9·0)	74 (9·3)	77 (10·1)	80 (12·9)	84 (15·7)	82 (15·6)
SBP	136 (25·3)	158 (32·0)	166 (32·3)	174 (32·3)	173 (29·3)	185 (34·5)
DBP	80 (12·1)	92 (15·4)	94 (16·7)	100 (10·6)	99 (12·7)	98 (15·7)
Normal control group.						
Heart rate	65 (8·1)	68 (6·9)	71 (9·9)	72 (9·3)	72 (8·3)	75 (11·8)
SBP	117 (16·5)	128 (15·3)	136 (17·5)	142 (22·8)	153 (29·9)	149 (22·8)
DBP	67 (15·4)	76 (15·1)	78 (15·0)	80 (14·9)	89 (15·7)	85 (20·4)

SBP, systolic blood pressure; DBP, diastolic blood pressure.
Results are expressed as mean (SD).

Table 3 *Comparative mean heart rate (beats/min) and blood pressure (mm Hg) responses to cold pressor test in subjects with coronary artery disease (group 2, n = 20) and a normal control group (group 1, n = 16)*

	Time from immersion of hand in ice (min)					
	Basal	*1*	*2*	*3*	*4*	*5*
CAD group:						
Heart rate	68 (9·4)	74 (10·0)	75 (12·1)	73 (8·6)	74 (10·2)	73 (10·4)
SBP	138 (25·3)	171 (37·1)	174 (35·2)	160 (26·7)	164 (36·0)	172 (40·2)
DBP	80 (11·2)	99 (14·1)	96 (14·1)	94 (12·2)	94 (13·5)	92 (8·2)
Normal control group:						
Heart rate	63 (7·8)	66 (9·6)	69 (10·5)	69 (10·0)	65 (10·2)	65 (8·2)
SBP	119 (13·9)	148 (26·2)	156 (25·3)	156 (27·1)	153 (26·1)	154 (21·6)
DBP	69 (9·5)	89 (20·2)	88 (15·9)	84 (17·1)	87 (11·7)	79 (17·6)

SBP, systolic blood pressure; DBP, diastolic blood pressure.
Results are expressed as mean (SD)

first 1–2 minutes after immersion and in the first few minutes after withdrawal. Groups 1 and 2 were similar in terms of age and resting heart rate, but both resting systolic and diastolic blood pressure were higher in those with coronary artery disease (table 1).

HEART RATE AND BLOOD PRESSURE

Both the heart rate and systolic blood pressure rose significantly in response to the sustained isometric handgrip exercise (table 2) and cold pressor test (table 3) at each minute during these interventions. There was a mean increase of 21% in heart rate in group 2 in response to sustained isometric handgrip exercise at the five minute stage, but there was only a 15% increase in response in group 1 (normals). Similarly, there was a mean increase of 36% in systolic blood pressure in group 2, but only a 27% increase in group 1; however, diastolic blood pressure increased to a similar extent in both groups.

During the cold pressor test those with coronary artery disease (group 2) increased their heart rate by a mean maximum of 10% and the systolic blood pressure by 26%. In the controls (group 1) these variables increased by 10% and 31% respectively; diastolic blood pressure increased by a similar degree in both groups (table 3).

The maximum increase (mean (SD)) in heart rate during sustained isometric handgrip exercise was 14 (11) beats per minute ($p < 0{\cdot}001$) in those with coronary artery disease (group 2) and 14 (13) beats per minute ($p < 0{\cdot}01$) in the normal subjects (group 1); the difference between groups was not statistically significant. Systolic blood pressure increased by a mean (SD) of 51 (18) mm Hg in those with coronary artery disease ($p < 0{\cdot}001$) and by 38 (21) mm Hg in controls ($p < 0{\cdot}01$); the difference was not statistically significant.

During the cold pressor test, heart rate increased by a maximum of 10 (10) beats per minute in those with coronary artery disease (group 2) and by 8 (6) in controls (group 1); this difference between groups was not statistically significant. Systolic blood pressure increased by a mean of 39 (18) mm Hg ($p < 0{\cdot}001$) in those with coronary artery disease and by 44 (23) ($p < 0{\cdot}001$) in controls; the difference in response between the groups was not significant.

During sustained isometric handgrip exercise, heart rate and systolic blood pressure rose in all subjects. During the cold pressor test, heart rate fell in one subject with coronary artery disease and in two controls. Systolic blood pressure rose in all subjects.

Sustained isometric handgrip exercise caused greater heart rate and blood pressure responses than the cold pressor test, but these differences were not statistically significant. Maximal haemodynamic responses tended to occur 3–5 minutes into the sustained isometric handgrip exercise test and 1–3 minutes into the cold pressor test. The timing of these maximal responses was similar in groups 1 and 2.

In both tests the haemodynamic response was evident during the first minute and was maintained for the five minute period of imaging.

VARIABILITY OF EJECTION FRACTION DETERMINATIONS

We assessed the variability of ejection fraction measurements from two sequential resting studies in the 16 normal control subjects (group 1). The difference (1·25%) between the two means was not statistically significant (table 4). From the individual mean of the two resting values and knowledge of the pooled variance we calculated the 95% confidence limits for a significant change of a subsequent ejection fraction measurement from the equation:

$$\bar{x} \pm 2{\cdot}12\sqrt{S^2\,(1/n + 1)}$$

where x is the observed measurement, 2·12 is the t value taken from the distribution of t when the number of observations is 16 at the 5% significance level, S^2 is the pooled variance, and n is the number of resting observations per patient. Thus for the 16 subjects, $S^2 = 19{\cdot}6$ percentage units, $n = 2$, and the

Table 4 *Results of sequential resting radionuclide ventriculograms in 16 control subjects*

Variable	*Rest*$_1$	*Rest*$_2$	*Difference*
dVs/dt	−4·3 (0·46)	−4·3 (0·42)	NS
dVd/dt	4·0 (0·50)	3·94 (0·37	NS
EF	61·5 (8·21)	60·2 (11·42)	NS

−dVs/dt = maximum rate of negative change of ventricular volume with time (ventricular emptying) measured as end diastolic volume/second.
+dVd/dt = maximum rate of positive change of ventricular volume with time (ventricular filling) measured as end diastolic volume/second.
Results are expressed as mean (SD)

95% confidence interval for a given patient is estimated to be −11·49 ejection fraction percentage units. This implies that the individual change of ejection fraction in response to any intervention must be 12% (absolute value) or more to be regarded as significant at the 5% level of significance. Variations of less than 12% could be the result of physiological and statistical fluctuations. This implies that a value would have to be 12% below the normal mean value to be regarded as an abnormal ejection fraction.

The coefficient of variance between two resting studies was 5·1%, indicating satisfactory reproducibility. Table 4 summarises the results of sequential resting radionuclide ventriculography studies in the normal subjects. No statistically significant differences for any variable were seen between the two resting studies. Linear regression analysis of ejection fraction response gave a correlation coefficient of 0·85 between the two resting studies.

The patients recruited into group 3 underwent three separate studies, with the first and second and the second and third 3 and 6 months apart respectively. Table 5 shows the responses to sustained isometric handgrip exercise and a cold pressor test. The coefficient of variance was 10% for sustained isometric handgrip exercise and 9% for cold pressor test, indicating satisfactory reproducibility.

RADIONUCLIDE VENTRICULOGRAPHY

Table 6 summarises the results of radionuclide ventriculography in groups 1 and 2 in response to sustained isometric handgrip exercise and a cold pressor test. In both groups the mean left ventricular ejection fraction fell in response to sustained isometric handgrip exercise and a cold pressor test. In normal subjects this fall was significant for only cold pressor testing. Both the cold pressor test and sustained isometric handgrip exercise tended to reduce dVs/dt.

Figures 1 and 2 show the group and individual changes in left ventricular ejection fraction in both groups 1 and 2 in response to both interventions. Sustained isometric handgrip exercise caused a mean (SD) reduction of 5 (8·3)% in those with coronary artery disease and a reduction of 4 (6·5)% in controls. This difference was not statistically significant. The cold pressor test caused a mean reduction of 10 (8)% in those with coronary artery disease and a reduction of 7 (5·6)% in controls; this

Table 5 *Coefficient of variance for ejection fraction response to sustained isometric handgrip (SIHG) and cold pressor test (CPT)*

	S$_1$	*S*$_2$	*S*$_3$	*Mean SD*
SIHG:				
Column mean (SD)	49 (12·2)	51 (11·8)	51 (13·1)	5·04
Overall mean		50·3		
Mean SD − overall mean (%)		Coefficient of variance = 10·02%		
CPT:				
Column mean (SD)	47 (9·7)	48 (9·8)	48 (12·8)	4·29
Overall mean		47·67		
Mean SD − overall mean (%)		Coefficient of variance = 8·99%		

S_{1-3} = studies 1–3

Table 6 *Results of radionuclide ventriculography during sustained isometric handgrip (SIHG) and cold pressor test (CPT) in 16 controls and 20 patients with coronary artery disease (CAD)*

	Rest	*SIHG*	*CPT*
Group 1 (controls):			
dVs/dt (ED vol/s)	−4·3 (0·42)	−3·9 (0·37)**	−3·9 (0·51)
dVd/dt (ED vol/s)	3·94 (0·37)	3·7 (0·35)*	3·9 (0·53)
EF	60·2 (11·42)	57·9 (10·18)	54·4 (10·64)***
Group 2 (patients with CAD and normal EF):			
dVs/dt (ED vol/s)	−4·6 (0·37)	−3·8 (0·61)***	−4·1 (0·48)***
dVd/dt (ED vol/s)	3·6 (0·48)	3·4 (0·74)	3·4 (0·57)
EF	60·7 (8·28)	55·7 (11·42)*	51·1 (9·96)

See table 4 for abbreviations.
*$p < 0·05$; ** $p < 0·01$; *** $p < 0·001$.
Results are expressed as mean (SD).

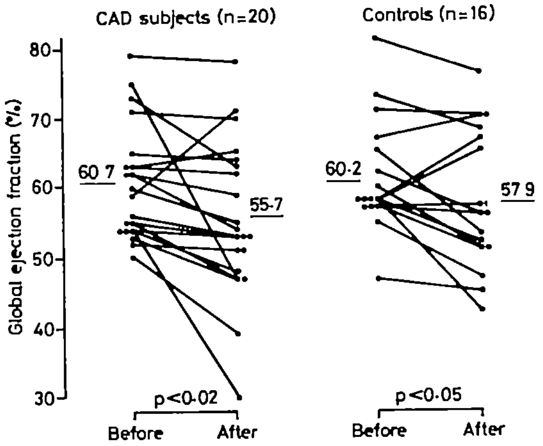

Fig 1 *Individual and group responses of the ejection fraction to sustained isometric handgrip in subjects with coronary artery disease (CAD) and a normal or near normal ejection fraction (group 2) and controls (group 1).*

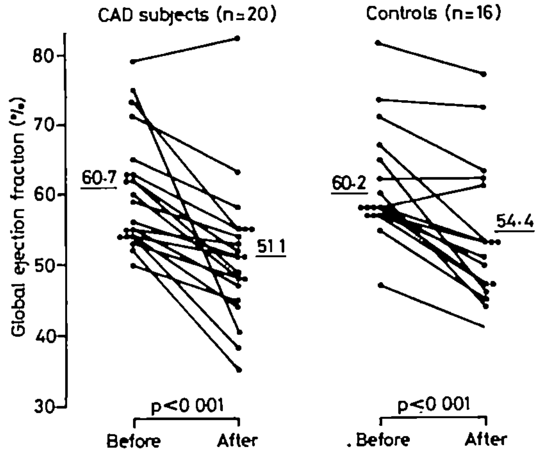

Fig 2 *Individual and group responses of ejection fraction to cold pressor test in subjects with coronary artery disease (CAD) and normal or near normal ejection fractions (group 2) and controls (group 1).*

difference between the groups was not statistically significant.

DETECTION OF CORONARY ARTERY DISEASE

Cold pressor testing caused a significant fall (≥12%) in ejection fraction in three controls and six patients with coronary artery disease. Thus the sensitivity for the detection of coronary artery disease was 30% and the specificity was 85%. In two controls and one subject with coronary artery disease the ejection fraction increased but not significantly.

Sustained isometric handgrip exercise caused a significant fall in ejection fraction in three patients with coronary artery disease, but there was no significant reduction in any of the controls. The ejection fraction increased in three controls and in two patients with coronary artery disease; the increase was significant in one patient from each group. Thus the sensitivity of the handgrip test for the detection of coronary artery disease was 15% and the specificity was 100%.

When both tests were combined the sensitivity increased to 35% and the specificity remained at 85%.

Discussion

The cold pressor test and sustained isometric handgrip exercise have been used in previous studies to unmask latent abnormalities of left ventricular function and to aid in the diagnosis of coronary artery disease.[6 7 10 17 21–25] The reproducibility of the responses to these interventions has not been adequately assessed. We have found these interventions to be useful for comparative studies because of their ease of application and ability to stress the myocardium without inducing angina pectoris or ST segment changes indicative of ischaemia. In comparison, dynamic exercise tends to cause these phenomena in a high proportion of subjects undergoing radionuclide ventriculography.[6] Both tests were simple and accessible and they were less cumbersome and time consuming than dynamic exercise.

COLD PRESSOR TEST

Heart rate and blood pressure

In patients with coronary artery disease and in normal controls heart rate increased by a mean of 10% in both groups and systolic pressure increased by 26% and 31% respectively. All these increases were statistically significant; but there were no significant differences between the two groups. Previous studies (table 7) have shown increases in heart rate ranging from +4 beats per minute[22] to +12 beats per minute[7 10] in normal subjects and +1[25] to +10[10] in patients with coronary artery disease. Systolic blood pressure rises in the present study were higher in both normal controls and subjects with coronary artery disease than in previous studies. There is no obvious explanation for this. Only one of our subjects (aged 54 years) with coronary artery disease was considered to have hypertension (184/103 mm Hg at rest). Most studies have reported that changes in blood pressure and heart rate in controls and patients with coronary artery disease are similar (table 7); and we too found no significant difference in response between these groups. Rootwelt *et al*[22] and Raizner *et al*[26] did not find a significant change in heart rate in normal subjects in response to the cold pressor test.

Table 7 *Comparison of studies that used cold pressor test in conjunction with radionuclide ventriculography*

	Normal group				*CAD group*					
	No	*HR (beats/min)*	*SBP (mm Hg)*	*EF (%)*	*No*	*HR (beats/min)*	*SBP (mm Hg)*	*EF (%)*	*Sensitivity (%)*	*Specificity (%)*
Wainwright *et al*[6]	22	NA	NA	+2	24	NA	NA	−13	79	100
Manyari *et al*[17]	20	+8	+26	+3	20	+9	+30	−5	55	95
Wasserman *et al*[10]	12	+11	+27	−6	18	+10	+22	−5	NA	NA
Vojacek *et al*[25]	10	+5	+13	−3	12	+1	+29	−5	NA	NA
Verani *et al*[7]	18	+11	+28	0	34	NA	NA	−6	NA	NA
Dymond *et al*[27]	12	+12	+16	−5	12	+9	+29	−8	NA	NA
Rootwelt *et al*[22]	11	+4	NA	+2	22	+6	NA	−3	50	100
Present study	16	+8	+44	−7	20	+14	+39	−10	50	37 5

HR, heart rate; SBP, systolic blood pressure; EF, ejection fraction; NA, not available.
Results expressed are mean value for each variable

This variability of heart rate and systolic blood pressure response in these studies may be because the cold pressor test was differently applied in different studies. In the present study, the hand was immersed in iced water (0–2°C) up to the level of the styloid process and the ice and water mixture was stirred continuously to maintain a constant adequate cold stimulus; also a fresh ice and water mixture was prepared for each patient. If this is not done the cold stimulus may be inadequate; this may explain the early decay in haemodynamic response reported by Dymond *et al*[27] but not by others.[6 10] The haemodynamic response to the cold pressor test reaches a maximum 60–90 seconds after immersion and basal values are quickly restored after the hand is withdrawn.[6 28–30] In our patients the haemodynamic responses were evident throughout the five minutes of imaging although some decay was noted after three minutes.

The haemodynamic changes are mediated by a predominantly α adrenergic stimulus[31] and an increase in systemic and pulmonary vascular resistance.[28 32] These haemodynamic changes increase myocardial oxygen consumption. Such changes may be enough to precipitate ischaemia in those with pre-existing coronary artery disease.

Radionuclide ventriculography

The cold pressor test induced significant falls in left ventricular ejection fraction in both normal subjects and patients with coronary artery disease; the difference between the two groups was not statistically significant. Two previous studies have reported falls in the ejection fraction in response to the cold pressor test,[10 25] whereas others have noted no change or a small increase.[6 7 17 22] In contrast, all studies consistently report falls in ejection fraction in patients with coronary artery disease. These range from a mean of −3 to −13% (table 7).

Thus the response to cold pressor test in normal subjects is inconsistent. This may be explained by differences in study protocol—in some studies images were collected for two minutes[17] and in others for five minutes,[6] in the latter study imaging was delayed for one minute. Dymond *et al* used sequential first pass radionuclide ventriculography during cold pressor test. They found that the ejection fraction fell significantly in both controls and those with coronary artery disease after one minute; but this fall was maintained at 2 5 and 4 minutes only in those with coronary artery disease.[27] In both groups the maximum reduction in ejection fraction occurred after one minute, despite the rise in blood pressure reaching a maximum after 2·5 minutes. They postulated that changes in afterload induced by cold pressor test are not the only reason for changes in left ventricular function. They concluded that left ventricular function changes rapidly during a period of cold stimulation, and that if the prime purpose is to detect coronary artery disease it would be prudent to delay the onset of imaging for one minute because normal subjects will be less likely to show a fall in ejection fraction after this. We started imaging after 30 seconds because this had been the practice of others who have assessed the cold pressor test under similar circumstances.[7 10 17 25]

SUSTAINED ISOMETRIC HANDGRIP EXERCISE

Heart rate and blood pressure

Heart rate rose more during this test than during the cold pressor test. It increased by a mean of 14 beats per minute both in patients with coronary artery disease and in normal controls. The increase in systolic blood pressure was also greater (by 51 and 38 mm Hg respectively). These changes are consistent with previous reports of increases ranging from 15% to 40%.[33 34] Bodenheimer *et al*, using a protocol similar to ours, observed blood pressure increases of 32 mm Hg in normal subjects and 33–44 mm Hg in patients with coronary artery disease.[8] In the present study the pronounced rise in heart rate and blood pressure was maintained for the five minute imaging period and the pattern of the response tended to be a sequential rise with little decay in the response, unlike the response to the cold pressor test. This was also the experience of Lind *et al* who found that blood pressure increased as fatigue developed.[35] In those with normal hearts an increase in blood pressure is primarily the result of an increase in cardiac output.[36] When the left ventricle is impaired the rise in blood pressure can be enhanced by an increase in systemic vascular resistance caused by stimulation of the adrenergic receptors by a fall in cardiace output.[36]

Radionuclide ventriculography

Although sustained isometric handgrip exercise caused a fall in ejection fraction in normal subjects this did not reach statistical significance, unlike the response to cold pressor test. The falls in ejection fraction experienced in those with coronary artery disease were significant, however. Bodenheimer *et al* found that in normal subjects the ejection fraction increased by a mean of 3% and in those with coronary artery disease it fell by 4% ($p < 0.005$),[21] yielding 86% sensitivity and 87% specificity for the detection of coronary artery disease. The present study demonstrated a sensitivity of 15% and a specificity of 100%. Others have reported that mean ejection fraction does not change in normal subjects[37]; however, individual normal subjects may have falls of 5% or more.[37 38]

It is possible that individuals with coronary artery disease will respond by a significant reduction in ejection fraction either to the cold pressor test or to the sustained isometric handgrip exercise but not to both. When the results of both tests were combined, however, the sensitivity improved to only 35%.

Variability of ejection fraction responses

Because we used a fully automatic method of analysing radionuclide ventriculograms we eliminated intra- and interobserver variation.

Two sequential resting studies in the normal controls gave a coefficient of variance of 5% and a correlation coefficient of 85%. No significant differences were found between studies for any indices of left ventricular function. In addition, the results were used to calculate the absolute change from normal that would be regarded as significant in our laboratory. The spontaneous variability in ejection fraction of 12% or more that we used to exclude non-random physiological change is more than that found in some laboratories[6 12 37] but comparable to others.[39]

In patients with normal left ventricular performance there is greater ventricular reserve and hence a greater probability of responding to stimuli with augmentation of cardiac pump function.[39] In those with subnormal basal ventricular performance, the ventricle may already be working at close to maximal effort and will therefore be less likely to manifest comparable spontaneous fluctuations in ejection fraction. Thus the variability in our repeat studies in normal subjects is probably higher than the variability that would be shown by a group of patients with coronary artery disease. In the present study large (up to 13%) individual interstudy differences were noted although the mean difference between the first and second study was −1·2 (6·16). Large individual changes (up to 21%) with a mean change of +4·6 (4·70) were reported by Wackers *et al* in a similar study population.[39]

The responses to both the cold pressor test and sustained isometric handgrip exercise had an acceptable reproducibility, with coefficients of variance of 9% and 10% respectively and no significant differences in the mean response on three separate occasions. This indicates that these interventions are suitable for studies of changes in left ventricular performance over time. In this respect both interventions are suitable alternatives to dynamic exercise.

DETECTION OF CORONARY ARTERY DISEASE

Wainwright *et al* claimed a sensitivity of 79% and specificity of 100% for the cold pressor test in detecting coronary artery disease (table 7).[6] In that study a change of 8% in ejection fraction was regarded as abnormal, although from their data there does not seem to be any clear reason for this limit. All normal subjects increased their ejection fraction by a mean of 2% in response to cold pressor test. These findings are unexpected because ventricular performance, even in normal subjects, is not enhanced by an increase in left ventricular afterload or systemic vascular resistance.[3 40]

In the present study, no normal subject had an increase in ejection fraction during the cold pressor test and three had significant (>12%) falls in ejection fraction. Although the mean fall in ejection fraction was greater in patients with coronary artery disease, the sensitivity (30%) and specificity (38%) in this group showed that in our laboratory and with this protocol the cold pressor test is not a useful intervention for the detection of coronary artery disease. It is possible that the responses obtained in these controls may reflect the presence of subclinical cardiomyopathy, intervention induced coronary artery spasm in the absence of symptoms or electrocardiogram changes, asymptomatic coronary artery disease, or a normal variation. But this was a group of symptom free lifelong non-smokers with no other major coronary artery disease risk factors. Each had a normal chest *x* ray and resting and treadmill exercise electrocardiogram, and all were presumed to have normal hearts. The study is open to criticism because coronary arteriography was not performed to exclude coronary artery disease, but in our unit the main indication for coronary arteriography is for the preoperative assessment of patients with angina pectoris; invasive investigation of our control group was not ethically justifiable.

Several studies have assessed the value of cold pressor test in detecting coronary artery disease. In studies comparing it with dynamic exercise Manyari *et al*[17] and others[7 22 25] have found it to be an inferior discriminator although possibly useful in subjects who are unable to perform dynamic exercise.

Though the sustained isometric handgrip exercise test produced greater increases in heart rate and blood pressure than the cold pressor test, it was only successful in detecting three subjects with coronary artery disease and gave a sensitivity of only 15%. The specificity was more acceptable, however. Several studies that compared sustained isometric handgrip exercise with dynamic exercise showed that it was of limited value in the detection of coronary artery disease.[41-43] In contrast, Bodenheimer *et al*, using radionuclide ventriculography, found a sensitivity of 86% and specificity of 87%.[8 21] These findings are of limited value, however, because most of their subjects had abnormalities at rest.

Some authorities have suggested that a patient may respond to only one or the other of these tests and that both should be performed. Our results do not support this because when both tests were combined the sensitivity for the detection of coronary artery disease was only 35%.

Conclusions

This study has demonstrated satifactory reproducibility of resting radionuclide ventriculography in a control group and of cold pressor test and sustained isometric handgrip exercise in a group with coronary artery disease. Significant heart rate and blood pressure responses were seen in both normal subjects and those with coronary artery disease; increases were higher with sustained isometric handgrip exercise.

Both cold pressor test and sustained isometric handgrip exercise are useful for serial comparisons of myocardial performance—for example the assessment of the effect of drugs on the myocardium. Coronary artery disease is not reliably detected if the left ventricular ejection fraction alone is used; however, when dynamic exercise is not possible these tests may be used as alternatives. In our laboratory the sensitivity was inadequate in patients with coronary artery disease who had normal or near normal resting electrocardiograms. Patients with coronary artery disease may not be able to complete an adequate dynamic exercise test without precipitating angina. Neither the cold pressor test nor sustained isometric handgrip exercise caused angina in our patients with coronary artery disease. One major advantage of cold pressor test and sustained isometric handgrip exercise is their ease of application without the risk of patient movement or excessive use of camera time. These factors are of obvious importance when serial evaluations are necessary.

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References

1 Ross J Jr, Braunwald E. The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. *Circulation* 1964;29: 739–49.

2 Payne M, Horowitz LD, Mullins CM. Comparison of isometric exercise and angiotensin infusion as stress test for evaluation of left ventricular function. *Am J Cardiol* 1973;31:428–33.

3 Mahler F, Ross J Jr, O'Rourke RA, *et al*. Effects of changes in preload, afterload and inotropic state on ejection and isometric phase measures of contractility in the conscious dog. *Am J Cardiol* 1975;35:626–34.

4 Parker JO, Khaja F, Case RE. Analysis of left ventricular function by atrial pacing. *Circulation* 1976;43: 241–52.

5 Chandraratna PAN, Shah PM, Kramer DH, Davis RJ, Schreiner BF. Spectrum of haemodynamic responses to atrial pacing in coronary artery disease. *Br Heart J* 1973;35:1033–40.

6 Wainwright RJ, Brennand-Roper DA, Cueni TA, Sowton E, Hilson AJW, Maisey MN. Cold pressor test in detection of coronary heart disease and cardiomyopathy using technetium 99m gated blood pool imaging. *Lancet* 1979;ii:320–3.

7 Verani MS, Zacca NM, DeBauche TL, Miller RR, Cahlne RA. Comparison of cold pressor and exercise radionuclide angiocardiography in coronary artery disease. *J Nucl Med* 1982;23:770–6.

8 Bodenheimer MM, Banka VS, Fooshee OM, Hermann GA, Helfant RH. Comparison of wall motion and regional ejection fraction at rest and during isometric exercise: concise communication. *J Nucl Med* 1979; 20:724–32.

9 Stefadouros MA. Isometric exercise training. Usefulness and limitations. *Arch Intern Med* 1983;143: 26–7.

10 Wasserman AB, Reiss L, Katz RJ, *et al*. Insensitivity of the cold pressor stimulation test for the diagnosis of coronary artery disease. *Circulation* 1983;67· 1189–93.

11 Kivowitz C, Parmley WW, Donoso E, Marcus H, Ganz W, Swan HJC. Effects of isometric exercise on cardiac performance. The grip test. *Circulation* 1971; 64:994–1002.

12 Helfant RH, DeVilla MA, Meister SG. Effects of sus-

tained isometric handgrip exercise on left ventricular performance. *Circulation* 1971;**44**:982–93.

13 Bruce RA, Gey GO, Cooler MN, Fisher LD, Peterson DR. Seattle Heart Watch: initial clinical, circulatory and electrocardiographic responses to maximal exercise. *Am J Cardiol* 1974;**33**:459–69.

14 Pavel DG, Zimmer AM, Patterson VN. In vivo labelling of red blood cells with 99m Tc: a new approach to blood pool visualisation. *J Nucl Med* 1977;**18**:305–8.

15 Goris ML, McKillop JH, Briandet PA. A fully automated determination of the left ventricular region of interest in nuclear angiography. *Cardiovasc Intervent Radiol* 1981;**4**:117–23.

16 Goris ML, Briandet PA. *A clinical and mathematical introduction to computer processing of scintigraphic images*. New York: Raven Press, 1983:3–19, 127–69.

17 Manyari DE, Nolewajka AJ, Purves P, Donner A, Kostuk WJ. Comparative value of the cold pressor test and supine exercise to detect subjects with coronary artery disease using radionuclide ventriculography. *Circulation* 1982;**65**:571–9.

18 Northcote RJ, O'Donoghue J, Ballantyne D. Assessment of Hitachi HME-20 pulse and blood pressure monitor. *J Med Eng Technol* 1985;**9**.10–3.

19 Caldwell JH, Hamilton GW, Sorensen SG, Ritchie JL, Williams DL, Kennedy JW. The detection of coronary artery disease with radionuclide techniques: a comparison of rest-exercise thallium imaging and ejection fraction response. *Circulation* 1980;**61**:610–9.

20 Hamilton GW, Caldwell JH, De Rouen TA, Williams DL, Ritchie JL, Sorensen SG. Serial measurement of ejection fraction by radionuclides: a methodologic and statistical approach [Abstract]. Proceedings of the World Federation of Nuclear Medicine and Biology, 1978;53:2.

21 Bodenheimer MM, Banka VS, Fooshee CM, Gillespie JA, Helfant RH. Detection of coronary heart disease using radionuclide determined regional ejection fraction at rest and during handgrip exercise: correlation with coronary arteriography. *Circulation* 1978;**58**. 640–8.

22 Rootwelt K, Erikssen J, Nitter-Hauge S, Thaulow E. Detection of coronary artery disease with gated cardiac blood-pool scintigraphy: comparison of cold pressor test and dynamic exercise. *Clin Physiol* 1982;**2**.459–65.

23 Gondi B, Nanda NC. Cold pressor test during two-dimensional echocardiography: usefulness in detection of patient with coronary artery disease. *Am Heart J* 1984;**107**:278–85.

24 Seneviratne BIB, Linton I, Wilkinson R, Rowe W, Spice M. Cold pressor test in diagnosis of coronary artery disease. echophonocardiographic method. *Br Med J* 1983;**286**:1924–6.

25 Vojacek J, Hannan WJ, Muir AL. Ventricular response to dynamic exercise and the cold pressor test. *Eur Heart J* 1982;**3**:212–22.

26 Raizner AE, Chahine RA, Ishimosi T, Verani MS, Zacca N. Provocation of coronary artery spasm by the cold pressor test. *Circulation* 1980;**62**·925–32.

27 Dymond DS, Caplin JL, Flatman W, Burnett P, Banim S, Spurrell R. Temporal evolution of changes in left ventricular function induced by cold pressor stimulation. An assessment with radionuclide angiography and gold 195m. *Br Heart J* 1984;**51**:557–64.

28 Green MA, Boltaxk AJ, Lustig CA, Rogow E. Circulatory dynamics during the cold pressor test. *Am J Cardiol* 1965;**16**:54–60.

29 Thacker EA. A comparative study of normal and abnormal blood pressures among university students, including the cold pressor test. *Am Heart J* 1940;**20**:89–97.

30 Godden JO, Roth GM, Hines ES. The changes in the intra-arterial pressure during immersion of the hand in ice-cold water. *Circulation* 1955;**12**:963–73.

31 Abboud FM, Eckstein JW. Reflex vasoconstrictor and vasodilator responses in man. *Circ Res* 1966;**18**(suppl I):1–96.

32 Boyer JT, Fraser JR, Doyle AE. The haemodynamic effects of cold immersion. *Clin Sci* 1960;**19**:539–50

33 Quarry VM, Spodick DH. Cardiac response to isometric exercise. Comparative effects with different postures and levels of exertion. *Circulation* 1974;**49**:905–20.

34 Laird WP, Fixler DE, Huffines FD. Cardiovascular response to isometric exercise in normal adolescents. *Circulation* 1979;**59**:651–4.

35 Lind AR, Taylor SH, Humphreys PW, Kennelly BM, Donald KW. Circulatory effects of sustained voluntary muscle contraction. *Clin Sci* 1964;**27**:229–44

36 Martin CE, Shauer AJ, Leon DF, Thompson ME, Reddy PS, Leonard JJ. Autonomic mechanisms in haemodynamic response in isometric exercise. *J Clin Invest* 1974;**54**:104–15.

37 Peter CA, Jones RH. Effects of isometric handgrip and dynamic exercise on left-ventricular function. *J Nucl Med* 1980,**21**:1131–8.

38 Stratton JR, Halter JB, Hallstrom AP, Caldwell JH, Ritchie JL. Comparative plasma catecholamine and haemodynamic responses to handgrip, cold pressor and supine bicycle exercise testing in normal subjects. *J Am Coll Cardiol* 1983;**2**:93–104.

39 Wackers FJT, Berger HJ, Johnstone DE, *et al.* Multiple gated cardiac blood pool imaging for left ventricular ejection fraction: validation of the technique and assessment of variability. *Am J Cardiol* 1979;**43**:1150–66.

40 Bugge-Asperheim B, Kill F. Cardiac mechanism for regulating stroke volume during elevation of aortic blood pressure in dogs. *Scand J Clin Lab Invest* 1972:**30**:23–33.

41 Helfant RH, Banka VS, DeVilla MA, Pine R, Kabde V, Meister SG. Use of bicycle ergometry and sustained handgrip exercise in the diagnosis of presence and extent of coronary heart disease. *Br Heart J* 1973;**35**:1321–5.

42 Haissly JC, Messin R, Degre S, Andermoten P, Demaret P, Denolin H. Comparative response to isometric (static) and dynamic exercise in coronary disease. *Am J Cardiol* 1974;**33**:791–6.

43 Kerber RE, Miller RA, Najjar SM. Myocardial ischaemic effects of isometric, dynamic and combined exercise in coronary artery disease. *Chest* 1975;**67**:388–94.

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Sudden coronary death in Glasgow: nature and frequency of acute coronary lesions

M A EL FAWAL,* G A BERG,† D J WHEATLEY,† W A HARLAND*

*From the *Department of Forensic Medicine and Science, University of Glasgow and †University Department of Cardiac Surgery, Royal Infirmary, Glasgow*

SUMMARY A detailed pathological study of the coronary arteries was carried out on 130 random white subjects (91 male and 39 female) who died suddenly in the Glasgow area. In 30 there was a clearly defined cause of death that was not due to ischaemic heart disease. In eight subjects the cause of death was in doubt. Ninety two of the 130 showed coronary stenosis resulting in a loss of more than 75% of coronary artery cross sectional area and/or acute coronary events with no other cause of death. Of these 92 subjects considered to have died suddenly of ischaemic heart disease, 64% showed plaque rupture and thrombosis which occurred at sites of previous high grades of stenosis. Twenty two subjects had intraluminal thrombosis unrelated to plaque fissuring. Thirty eight (41%) showed histological evidence of recent myocardial necrosis; acute coronary events occurred in 34 of these. There was no correlation between the duration of symptoms before death and the occurrence of acute coronary events.

Acute coronary events, mainly in the form of plaque rupture, are a common finding in sudden coronary death when a careful study is made of the whole coronary arterial tree.

In view of the fact that atherosclerosis has been recognised for many years and the fact that ischaemic heart disease is so prevalent[1 2] it may seem surprising that controversy still surrounds the mechanism of sudden death from coronary disease. Severely diseased and narrowed coronary arteries may be compatible with many years of symptom free life[3] but when sudden death occurs in individuals with ischaemic heart disease the mechanism and triggering event are still in dispute.[4] Sudden death in the majority of subjects with ischaemic heart disease is attributed to cardiac arrhythmia, and previous pathological studies have suggested that the frequency of coronary thrombi and acute lesions is low.[5–7] Others have claimed that coronary thrombi are consequences rather than causes of myocardial infarction.[8 9] More recently, attention has been drawn to the importance of acute plaque events and the role of coronary thrombosis in sudden cardiac death.[10 11] In cases of sudden unexpected death pathological examination usually takes place as a medicolegal necropsy aimed primarily at excluding unnatural death. It is thus understandable that appropriate detailed pathological data from this source have been scanty. A study was therefore undertaken of 130 random cases of sudden death submitted to medicolegal necropsy in Glasgow with the aim of further clarifying the mechanism of death and of assessing the status of the coronary tree and myocardium.

Patients and methods

We studied 130 white subjects under the age of 70 (91 male and 39 female) who died suddenly in the Glasgow area and who were submitted to medicolegal examination at the Department of Forensic Medicine and Science of the University of Glasgow. Thirty subjects were identified who had a clear cause of death other than ischaemic heart disease. Ninety two had more than a 75% loss of coronary artery cross sectional area and/or an acute coro-

Requests for reprints to Professor D J Wheatley, Department of Cardiac Surgery, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER.

Professor W A Harland died on 9 January 1985

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nary lesion and no other cause of death. They therefore were considered to have died from ischaemic heart disease. The remaining eight had less severe coronary artery atherosclerosis (degrees of stenosis less than 75% of cross sectional area) and had no other clear cause of death.

Sudden death was defined as death occurring within 24 hours of the onset of symptoms in a subject who had not consulted a doctor at any time during the previous three weeks. Case notes were reviewed to determine the subject's activity at the time of onset of symptoms or death. A detailed necropsy was undertaken in each case, including histological study where necessary. When appropriate, toxicological examinations were undertaken to identify alcohol, carbon monoxide, or drug poisoning.

The heart was removed unopened for initial angiographic study. The right and left coronary arteries were selectively injected with a barium-gelatin mixture and radiographic delineation of the coronary vessels was obtained. The warm mixture was injected through a hand-held syringe until satisfactory filling of epicardial vessels was noted. The major epicardial coronary arteries were dissected from the fixed heart; then they were decalcified for five days and the radiographic study was repeated. The coronary arteries examined included the entire right coronary artery with its posterior descending and posterolateral branches; the left main coronary artery; the anterior descending coronary artery and its major diagonal branches; and the circumflex coronary artery and its marginal branches.

After postmortem angiography a low midventricular 2 cm transverse slice was cut. The level of the cut was sometimes changed according to the site of the infarct if any had been detected macroscopically. Nitroblue tetrazolium staining was used to complement routine histological examination.[12]

Histological blocks were then made at approximately 3 mm intervals in the major arteries and labelled for identification according to a standard code[13] (fig 1). Each histological section, stained with haematoxylin and eosin, was examined microscopically and coded for the presence of plaque fissuring and dissecting haemorrhage from the lumen, intraluminal thrombosis, intramural thrombosis, or old occlusion. Plaque fissuring or rupture was diagnosed when the intimal cap was disrupted and resulted in a free continuity between the atheromatous material and the lumen. Intraluminal thrombosis when present was recorded. An accumulation of red blood cells within the intima without fissuring or thrombotic material was designated as an intimal haemorrhage.

Each coronary section was measured by a quantitative microscope. The degree of stenosis was estimated by planimetry of the area within the internal elastic lamina (representing the original lumen) and the area of the existing lumen—the result being expressed as a percentage loss of cross sectional area. Thrombi when present were measured and their extent was expressed as a percentage of the lumen area before thrombosis had occurred.

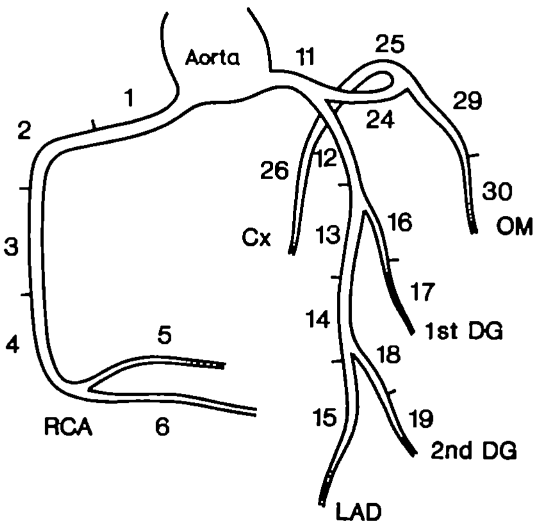

Fig 1 *Division of coronary tree into segments: right coronary artery (RCA), segments 1–6; left main coronary artery, segment 11; left anterior descending artery (LAD), segments 12–15; first and second diagonal branches (1st DG and 2nd DG), segments 16 and 17 and 18 and 19 respectively; circumflex artery (Cx), segments 24–26; obtuse marginal artery (OM), segments 29 and 30.*

Results

The results of our studies indicated that 92 subjects had died suddenly from ischaemic heart disease: they had one or more "significant" stenoses (defined for the purposes of this study as loss of more than 75% of cross sectional area), a recent coronary event or both, with no other identifiable cause for death (two had acute coronary events with lesions causing a 66%–72% loss of coronary artery cross sectional area). Of the 92 cases, 81 (88%) had acute coronary lesions and 11 had significant stenoses without associated acute lesions (fig 2).

NATURE OF THE ACUTE CORONARY LESIONS

Plaque rupture

Plaque rupture was found in 59 (73%) of the 81 subjects with acute coronary lesions. Thirty nine of these 59 (66%) subjects had associated intraluminal

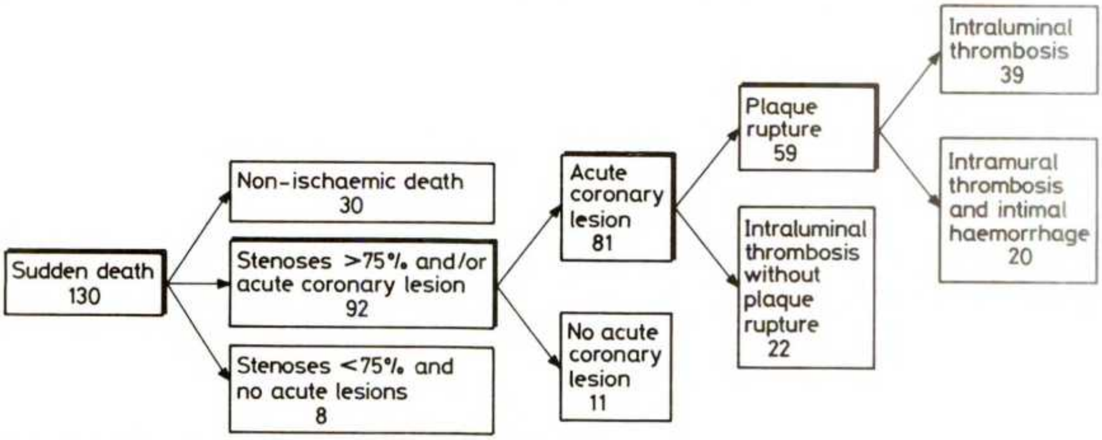
Sudden death 130
Non-ischaemic death 30
Stenoses >75% and/or acute coronary lesion 92
Stenoses <75% and no acute lesions 8
Acute coronary lesion 81
No acute coronary lesion 11
Plaque rupture 59
Intraluminal thrombosis without plaque rupture 22
Intraluminal thrombosis 39
Intramural thrombosis and intimal haemorrhage 20

Fig 2 *Distribution of coronary events in 130 victims of sudden death.*

thrombosis. There were 80 instances of plaque rupture in these 59 subjects—35 in the right coronary artery, 30 in the anterior descending coronary artery, and 15 in the circumflex artery. Figure 3 shows a typical example of plaque rupture. Plaque rupture and accompanying acute lesions were more common at sites with higher grades of pre-existing stenosis (table 1). Intraluminal thrombus was often found where there was stenosis of more than 75%.

Intraluminal thrombus

Intraluminal thrombi were found in 61 subjects. In 22 of these, no associated underlying fissuring could be identified. Seventy five separate thrombi were found: 48 were occluding more than 50% of the lumen and 27 occupied less than 50%. Figure 4 shows the appearance of a typical intraluminal thrombus associated with plaque fissuring. Table 2 shows the distribution and degree of thrombotic occlusion of the largest thrombus in each of the 61 subjects.

DISTRIBUTION OF THE ACUTE EVENTS

Figure 5 shows the distribution of plaque rupture in the different segments of the coronary tree. Certain segments, such as the second segment of the right coronary, the first three segments of the anterior descending branch, and the first two segments of the circumflex branch were the sites most affected by acute lesions.

Table 1 *Degree of pre-existing stenosis at sites of plaque rupture and the accompanying acute lesions (total 80 plaque ruptures)*

	Pre-existing stenosis		
Acute lesion	*<50%*	*50–75%*	*>75%*
Intimal haemorrhage and intramural thrombus	1	18	26
Intraluminal thrombosis	0	2	33

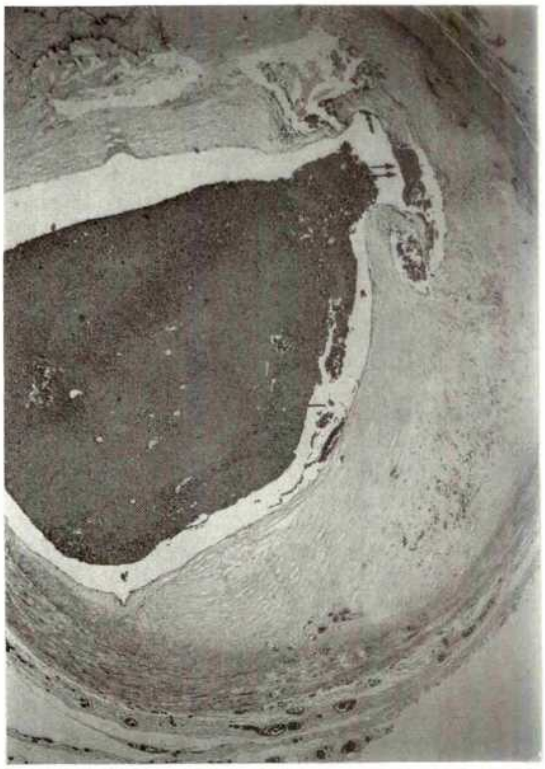

Fig 3 *Photomicrograph showing fissuring of an atheromatous plaque with resealing by a small mural thrombus (arrows).*

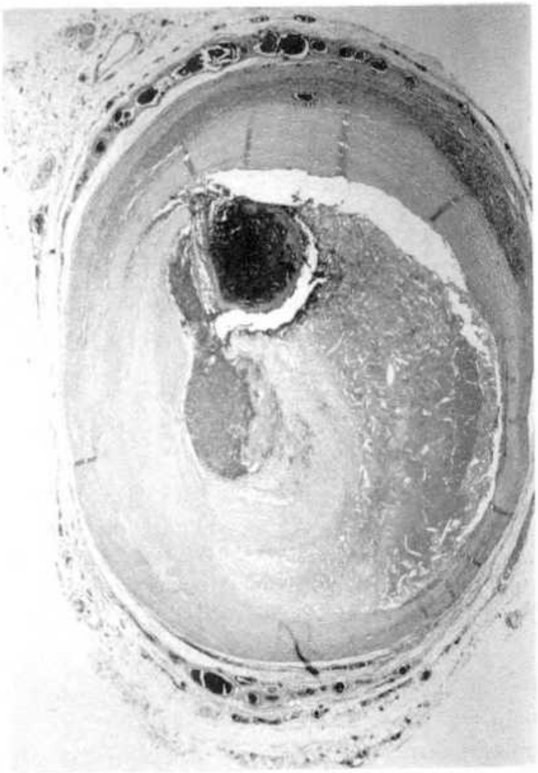

Fig 4 *Photomicrograph showing plaque rupture accompanied by both intraluminal and intramural thrombus. The affected vessel had an 88% loss of cross sectional luminal area and the luminal thrombus occupied 35% of the stenosed lumen.*

Table 2 *Degree of thrombotic occlusion caused by intraluminal thrombi in 61 victims of sudden cardiac ischaemic death*

Size of largest thrombus per case (% of lumen)	*Number of subjects*	*Coronary artery*		
		RCA	*LAD*	*Cx*
1–24	12	3	6	3
25–50	14	7	5	2
51–75	12	5	6	1
76–100	23	9	7	7
Total	61	24 (39%)	24 (39%)	13 (22%)

RCA, right coronary artery; LAD, left anterior descending artery; Cx, circumflex artery.

ACTIVITY AND DURATION OF SYMPTOMS

There was no correlation between the duration of symptoms before death and the occurrence of plaque rupture or intraluminal thrombus (tables 3 and 4). The occurrence of acute coronary lesions was not related to activity at the time of death (table 5).

STATUS OF THE MYOCARDIUM

The nitroblue tetrazolium method used in combination with routine histology showed that 38 (41%) of the 92 subjects in whom there was unequivocal evidence of coronary death had recent myocardial necrosis. Thirty four of these 38 showed evidence of acute coronary events. Table 6 summarises the findings in the subjects with myocardial necrosis.

Forty six (50%) subjects had old (or healed) myocardial infarctions. Twenty four of these had old lesions in one or more of the coronary arteries (recanalisation).

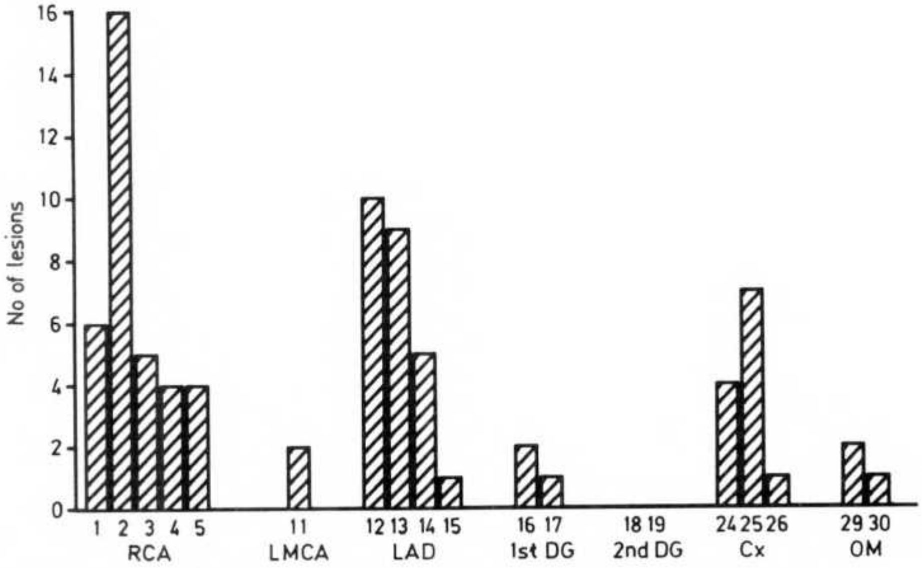

Fig 5 *Distribution of plaque rupture in 59 subjects (numbers indicate segments as shown in fig 1). RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery; 1st DG, first diagonal branch of LAD; 2nd DG, second diagonal branch of LAD; Cx, circumflex artery; OM, obtuse marginal artery.*

Table 3 *Relation of the interval between onset of symptoms and death to occurrence of plaque rupture (total number 92 subjects)*

Interval	*15 min*	*15–60 min*	*1–6 h*	*6–24 h*	*Unknown*
Number of subjects	31	11	11	11	28
Number with plaque rupture	20 (65%)	9 (82%)	6 (55%)	6 (55%)	18 (64%)

Table 4 *Relation of the interval between onset of symptoms or death to the presence of a thrombus (total number 92 subjects)*

Interval	*15 min*	*15–60 min*	*1–6 h*	*6–24 h*	*Unknown*
Number of subjects	31	11	11	11	28
Number with thrombus	20 (65%)	7 (64%)	8 (73%)	8 (73%)	18 (64%)

Table 5 *Relation of activity at time of death to presence of acute lesion (total number 92 subjects)*

Activity	*Luminal thrombosis*	*Plaque rupture with mural thrombosis or haemorrhage*	*No acute lesion*
Sleeping or sedentary (61 subjects)	42 (69%)	13 (21%)	6 (10%)
Moderate activity (15 subjects)	9 (60%)	3 (20%)	3 (20%)
Strenuous activity (16 subjects)	10 (63%)	4 (25%)	2 (12%)

Table 6 *Findings in 38 cases with recent myocardial necrosis*

Location of necrosis	*Number of infarcts*	*Right coronary event*	*Left anterior descending event*	*Left circumflex event*	*Recent event in more than one artery*	*Recent event in unexpected artery*	*No recent event*
Anterior	9	5	8	1	5	0	1
Lateral	3	1	0	2	0	0	0
Posterior	16	10	3	7	6	2	3
Circumferential	8	4	6	0	2	0	0
Septal	2	1	2	0	1	0	0

SUBJECTS IN WHOM THE CAUSE OF DEATH WAS IN DOUBT

Eight of the 100 subjects showed varying degrees of stenosis, between 20% and 73% (mean maximum stenosis 53%), without demonstrable acute coronary lesions and the cause of death must be considered to be in doubt. In common with a similar London study[14] these subjects were excluded from further analysis.

NON-ISCHAEMIC DEATHS

Table 7 shows the identified cause of death in the group of 30 subjects in whom a non-ischaemic cause of death was found. No intraluminal thrombosis was found in any of these 30 subjects. Plaque fissuring accompanied by intimal haemorrhage was, however, present in one (a victim of drug overdose).

Table 7 *Cause of death in 30 subjects who died of non-ischaemic causes*

Cause of death	*Number*
Respiratory disease	6
Cardiovascular (non-ischaemic)	6
Overdose	13
Infections	2
Cerebrovascular disease	2
Unknown cause	1

Discussion

The controversy about the frequency of coronary thrombi and plaque rupture in sudden ischaemic death is unresolved, with various groups reporting markedly different findings.[8 14 15] The data reported in the present study indicate that in 88% of subjects where death occurred suddenly from ischaemic heart disease there was a recent lesion in one or more of the coronary arteries. The findings in this study resemble those of a recent similar study by Davies and Thomas.[10] Both studies confirm that when a careful and detailed examination of the whole epicardial coronary tree is made acute lesions are often found. This study has demonstrated the nature and frequency of acute coronary events in sudden death from ischaemic heart disease. Pathological examination, however, cannot determine the precise pathophysiological mechanisms involved—low cardiac output (pump failure) or arrhythmia (ventricular fibrillation).

Plaque rupture or fissuring has been recognised by pathologists for many years,[16-18] yet it is still not widely appreciated that rupture of the soft lipid rich plaque is a major and common life-threatening event. The degree of pre-existing stenosis appears to play a decisive role in the sequelae of plaque fissuring. When there is rupture of a plaque that occupies <75% of the cross sectional area of the artery intimal haemorrhage without thrombosis is frequently found. When the plaque causes stenosis >75% of the cross sectional area its rupture is often associated with thrombosis. This accords with the findings of Falk.[19]

This study of sudden death shows that plaque fissuring is more common in certain segments of the coronary tree than in others. These segments, however, were also the sites of higher grades of stenosis and highest frequency of thrombosis, and therefore anatomical site by itself probably does not determine the likelihood of plaque rupture. Plaque rupture seems to be an important part of the atherosclerotic process which may result in acute vessel occlusion and its outcome is determined to a great extent by the degree of pre-existing stenosis. If the pre-existing stenosis is severe, acute vessel occlusion will occur; less severe stenosis may only result in an increase in plaque size. The size of the cracked intimal cap and the platelet response at the site of rupture also play an important role in determining the nature of the lesion accompanying the rupture.[4 19] This study confirms that intraluminal thrombosis is a common finding in segments of coronary artery in which there is plaque rupture.

Our study has identified a subgroup in the 92 subjects who died suddenly from ischaemic heart disease in whom no acute coronary lesion could be identified. This group of 11 subjects with definite ischaemic heart disease but no acute coronary lesion showed stenosis producing more than 75% loss of luminal cross sectional area in at least one major coronary artery. Although we cannot rule out the possibility of missing a small area of plaque fissuring or a tiny thrombus there are other possible mechanisms for sudden cardiac death. These include platelet microthrombi, coronary artery spasm, myocardial oxygen supply/demand imbalance, or disturbances of rhythm.

Acute lesions in the proximal coronary arteries may produce larger areas of ischaemic myocardium and are more likely to cause death. This seems to accord with the clinical and angiographic findings when severely stenosed proximal arteries are bypassed by grafts and long term survival is improved.[20]

Local vascular spasm precipitated by plaque rupture is another possible explanation for the mechanism of death, as is a large mural thrombus bulging into the lumen and obstructing the vessel in the absence of associated intraluminal thrombosis.[10] Another possibility is that there may have been spontaneous lysis of intraluminal thrombus antemortem.[3]

The relatively low frequency of demonstrable myocardial infarction in the present study (41%) must in part reflect the sudden nature of death, as the nitroblue tetrazolium test and conventional histology do not detect infarction where the survival period is short.[12]

Acute coronary lesions were a common finding in cases with recent myocardial necrosis and in all cases except two they occurred in the artery supplying the area of infarction. In cases with diffuse subendocardial infarction significant stenoses were noted in all three major coronary vessels. The study also showed that in about half the cases with healed infarcts the ischaemic damage was probably due to an old coronary event. This was suggested by the presence of recanalisation in the supplying artery in 24 of the 46 cases with old infarcts.

This study provides no evidence of an association between the occurrence of acute coronary lesions and the interval between the onset of symptoms and time of death. Others have claimed that acute coronary lesions are not found in subjects dying instantaneously from ischaemic heart disease.[21 22] It was also claimed that the longer the duration of survival after the onset of symptoms, the more frequently are acute lesions present. Our study does not confirm claims that plaque rupture is more commonly the underlying fatal event in older rather than younger patients[15]; however, we found a higher frequency of intimal haemorrhage accompanying the rupture in the older group. Furthermore, our study has shown no association between the activity at the time of death and the presence of acute coronary events. This finding does not contradict the possibility that sudden unaccustomed activity may precipitate sudden coronary death. It is possible, however, that the sudden rupture of the thin fragile cap may require no more than normal haemodynamic stresses.[19]

The importance of acute coronary lesions as the mechanism of sudden ischaemic death is emphasised by their absence in the majority of subjects who died of causes other than ischaemic heart disease (plaque fissuring was noted in only one of 30 such subjects). Circumferential myocardial infarction was present in two of these subjects and may be explained by pre-terminal hypotension, as one died of intracerebral haemorrhage and the other of a drug overdose.

The results of this study emphasise the importance of acute plaque events in atherosclerotic coronary arteries as the major cause of sudden cardiac death in Glasgow. The events take the form of plaque rupture and are commonly associated with thrombosis. The findings in this study and in a similar recent London study[10] suggest little difference between the two cities in the nature and frequency of acute coronary events occurring in those who die suddenly.

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References

1 Shaper AG, Cook DG, Walker M, Macfarlane PW. Prevalence of ischaemic heart disease in middle aged British men. *Br Heart J* 1984;**51**:595–605.

2 Shaper AG. Ischaemic heart disease—epidemiology and possibilities for primary prevention. *Medicine International* 1985;**2**:826–31.

3 Davies M. Ischaemic heart disease—the pathological basis. *Medicine International* 1985;**2**:821–5.

4 Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J* 1985;**53**:363–73.

5 Roberts WC, Buja LM. The frequency and significance of coronary arterial thrombi and other observations in fatal acute myocardial infarction. *Am J Med* 1972;**52**:425–43.

6 Schwartz CJ, Gerrity RG. Anatomical pathology of sudden unexpected cardiac death. *Circulation* 1975;**52**:18–26.

7 Warnes CA, Roberts WC. Sudden coronary death: comparison of patients with to those without coronary thrombus at necropsy. *Am J Cardiol* 1984; **54**:1206–11.

8 Baroldi G. Acute coronary occlusion as a cause of myocardial infarct and sudden coronary heart death. *Am J Cardiol* 1965;**16**:859–80.

9 Erhart LR, Unge G, Boman G. Formation of coronary arterial thrombi in relation to onset of necrosis in acute myocardial infarction in man. A clinical and autoradiographic study. *Am Heart J* 1976;**91**:592–8.

10 Davies MJ, Thomas A. Thrombosis and acute coronary artery lesions in sudden cardiac ischaemic death. *N Engl J Med* 1984;**310**:1137–40.

11 Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolization culminating in total vascular occlusion. *Circulation* 1985;**71**:699–708.

12 Nachlas MM, Schnitka TK. Macroscopic identification of early myocardial infarcts by alterations in dehydrogenase activity. *Am J Pathol* 1963;**43**:379–404.

13 Brandt PW, Partridge JB, Wattie WJ. Coronary arteriography: method of presentation of the arteriogram report and a scoring system. *Clin Radiol* 1977; **28**:361–5.

14 Lie JT, Titus JL. Pathology of the myocardium and the conduction system in sudden coronary death. *Circulation* 1975;**52** (suppl III):41–52.

15 Liberthson RR, Nagel EL, Hirschman JC, Nussenfeld SR, Blackbourne BD, Davis JH. Pathophysiologic observations in prehospital ventricular fibrillation and sudden cardiac death. *Circulation* 1974;**49**: 790–8.

16 Leary T. Pathology of coronary sclerosis. *Am Heart J* 1934;**10**:328–35.

17 Leary T. Coronary spasm as a possible factor in producing sudden death. *Am Heart J* 1934;**10**:338–44.

18 Constantinides P. Plaque fissures in human coronary thrombosis. *J Atheroscler Res* 1966;**6**:1–17.

19 Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *Br Heart J* 1983;**50**:127–34.

20 European Coronary Surgery Study Group. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet* 1982;**ii**:1173–80.

21 Friedman M, Manwaring JH, Rosenman RH, Donlon G, Ortega P, Grube SM. Instantaneous and sudden deaths; clinical and pathological differentiation in coronary artery disease. *JAMA* 1973;**225**:1319–28

22 Spain DM, Bradess VA. Sudden death from coronary heart disease: survival time, frequency of thrombi and cigarette smoking. *Chest* 1970;**58**:107–10.

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A double blind placebo controlled comparison of verapamil, atenolol, and their combination in patients with chronic stable angina pectoris

IAIN N FINDLAY, KAY MacLEOD, GERARD GILLEN, ALEX T ELLIOTT, THOMAS AITCHISON,* HENRY J DARGIE

*From the Department of Cardiology, Western Infirmary Glasgow, and the *Department of Statistics, University of Glasgow*

SUMMARY The efficacy and effect on cardiac function of verapamil 120 mg three times a day and atenolol 100 mg once a day, singly and in combination, were evaluated in 15 patients with angina pectoris. While they were on the combination treatment four patients withdrew from the study. Episodes of angina pectoris and glyceryl trinitrate consumption were significantly reduced only on the combination. On the combination only four patients developed evidence of ischaemia during exercise compared with seven on verapamil and ten on atenolol. ST segment depression at peak exercise, assessed by 16 point precordial mapping, was reduced by all active treatments from 7·1 on placebo to 2·7, 0·9, and 0·6 mm on atenolol, verapamil, and the combination respectively. Mean left ventricular ejection fraction fell significantly from 60% on placebo to 53% on the combination but was unchanged on verapamil and atenolol.

Verapamil was an effective alternative to atenolol; the combination was the most effective treatment but was associated with a significant morbidity.

Although β adrenoceptor blockers remain the mainstay for the treatment of effort related angina pectoris, in a considerable number of patients they may cause troublesome side effects, are only partially effective, or are relatively contraindicated.

Recently calcium antagonists have been introduced into the management of the various forms of angina pectoris including that related to effort.[1-3] The differing and possibly complementary actions of the β blockers and calcium antagonists raise the possibility that a combination of these two agents may have beneficial or detrimental interactions.[4] While it is generally accepted that the combination of the calcium antagonist nifedipine and a β blocker is safe in patients with normal ventricular function,[5-7] caution has been advised with the combination of verapamil and a β blocker because of the likely, and possibly detrimental, mutual potentiation of effects on cardiac conduction and contractility.[1 8 9] We have evaluated the effects of verapamil and atenolol, singly and in combination, on cardiac function in patients with stable angina.

Requests for reprints to Dr Iain N Findlay, National Heart Hospital, Westmoreland Street, London W1M 8BA

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Patients and methods

Fifteen patients (10 men) were recruited from the cardiology clinic of the Western Infirmary (table 1). All had chronic effort related angina pectoris with a stable pattern of symptoms for at least three months and none had pain at rest. All had an unequivocally positive exercise test for myocardial ischaemia ($\geq 0\cdot1$ mV ST segment depression occurring 80 ms after the J point) at the end of a two week single blind placebo run in period during which all other antianginal medication was withdrawn.

We excluded patients with appreciable chronic obstructive airways disease, severe hypertension (blood pressure > 170/110 mm Hg off all treatment), myocardial infarction within the previous three months, peripheral vascular disease, previous congestive cardiac failure, or evidence of pronounced conduction abnormalities on the electrocardiogram. Coronary arteriography was carried out in most patients after the study was completed.

TRIAL DESIGN

There were four treatment periods each lasting three weeks. They were placebo, verapamil 120 mg three times a day, atenolol 100 mg once a day, and the

Table 1 *Patient characteristics, exercise test (Bruce protocol), and coronary anatomy in patients with chronic stable angina*

	Age	*Sex*	*Previous infarct*	*Exercise time (min)*	*Treatment*	*Vessels with significant stenosis (>50% of luminal diameter)*
1	59	M	—	6·0	Nifedipine	Not known
2	55	M	—	7·3	Atenolol/nifedipine	LAD, Cx, 100% RCA
3	55	M	Inf	4·3	Oxprenolol	LAD, Cx, 100% RCA
4	53	F	Inf	6·0	Triple therapy	100% Cx, RCA
5	51	M	—	8·3	Metoprolol	LAD, Cx, 100% RCA
6	57	M	—	4·3	Nifedipine/nitrate	LAD, OM, 100% RCA
7	52	M	—	4·0	None	LAD, Cx, 100% RCA
8	62	F	n/t Ant	3·0	Atenolol	100% LAD, 100% Cx, RCA
9	60	F	—	5·0	Atenolol/nifedipine	LAD, Cx, RCA
10	58	M	Ant	4·0	Pindolol/nitrate	100% LAD, 100% RCA
11	65	M	—	3·0	Atenolol	Not known
				Withdrawn from study		
12	48	M	—	12·0	Metoprolol	LAD, Cx, RCA
13	44	F	—	6·0	None	OM, 1st diag
14	52	F	—	4·0	Atenolol/nifedipine	Cx, 100% RCA
15	54	M	—	4·0	None	LAD, 100% Cx, RCA

Ant, anterior; Inf, inferior; n/t, non-transmural, LAD, left anterior descending, Cx, circumflex; RCA, right coronary artery; OM, obtuse marginal; 1st diag, first diagonal. 100% = blocked.

combination. The order of administration was determined by a balanced latin square design, and the use of a double dummy technique ensured that all treatments were visually identical. At the end of each study period the following assessments were made.

Subjective data

Patients recorded the frequency of angina and consumption of glyceryl trinitrate on diary cards and each was asked to follow his or her normal daily routine throughout the trial. Moreover, patients were instructed to use glyceryl trinitrate for the treatment of acute attacks of angina but were asked to refrain from using it prophylactically.

Patients were asked about any important side effects and treatment preference.

Objective data

Heart rate and blood pressure—Heart rate and blood pressure were recorded after three minutes' recumbency and two minutes' standing and at the end of each exercise test.

Exercise testing: 16 point precordial electrocardiographic mapping—Patients exercised on an electronically braked bicycle ergometer. They started at 25 W and the workload was increased by 25 W every three minutes. Patients became familiar with the exercise test during three supine bicycle exercise tests performed while treatment was being withdrawn and before entry into the placebo run in period. Each patient's maximum workload was determined at the end of this period and thereafter he or she exercised to that workload. The number of points showing ≥1 mm planar ST segment depression (area of ischaemia) and the total ST segment depression were recorded immediately and at 1, 3, 5, and 10 minutes after exercise.[10] Heart rate and blood pressure were monitored throughout the test.

24 hour ambulatory electrocardiographic monitoring—Ambulatory monitoring was carried out with the Medilog I system. The tapes were analysed for mean hourly heart rate and for abnormalities of cardiac rhythm and conduction. The PR interval was recorded from a standard 12 lead electrocardiogram taken immediately before ambulatory monitoring.

Radionuclide ventriculography—Gated radionuclide ventriculography was carried out at rest and during the last two minutes of bicycle exercise. The blood pool was visualised after the patient's red blood cells had been labelled in vivo with 800 mBq of technetium-99m. Scintigraphic images were obtained by means of an Ohio series 100 single crystal gamma camera fitted with a high resolution parallel hole collimator, interfaced with a Varian computer.[5] In our department left ventricular ejection fraction obtained by radionuclide ventriculography correlated well with contrast angiography ($r = 0{\cdot}8$ $n = 32$); intraobserver reproducibility was high ($r = 0{\cdot}95$) and the standard error of the estimate was 3%.

Drug and catecholamine concentrations—Plasma concentrations of verapamil and nor-verapamil were measured in blood samples collected 2–4 hours after the last dose. Plasma atenolol concentration was measured 6–8 hours after the last dose.[11,12] Plasma noradrenaline (an index of peripheral sympathetic activity) was measured after the patient had been recumbent for 15 minutes.[13]

STATISTICAL ANALYSIS

This was performed by repeated measures analysis of variance across the four treatments. A Bonferroni correction for multiple comparisons was applied to allow for the possibility of spurious differences generated by the use of multiple *t* tests and an overall significance level of 5% was used.[14] The interpretation of the results is shown in the appendix.

The work done to the onset of angina pectoris and ST depression was analysed by log rank analysis.[15]

Results

Four patients withdrew from the study and are not included in the results. The study was analysed for a possible order or crossover effect but this was not apparent.

SUBJECTIVE

Angina pectoris and glyceryl trinitrate consumption

The mean frequency of angina pectoris was 30·0, 19·9, 16·8, and 7·6 episodes on placebo, atenolol, verapamil, and the combination respectively; only on the combination treatment was this reduction significant. Mean glyceryl trinitrate consumption was 37·1, 13·7, 9·0, and 5·9 tablets (all not significant). Patient number 10 experienced severe angina pectoris on placebo with over one hundred attacks many of which required two glyceryl trinitrate tablets for the relief of pain. Removal of this outlier from the analysis considerably reduced the average placebo values and also the estimate of overall variability of glyceryl trinitrate consumption from ±8·9 to ±2·4 and frequency of angina pectoris from ±4·3 to ±2·9; this reduction in variability leads to improved treatment comparisons (table 2). Overall the combination was the most effective treatment in reducing both the frequency of angina and glyceryl trinitrate consumption.

OBJECTIVE

Heart rate and blood pressure (tables 3 and 4)

Verapamil and atenolol given alone significantly reduced erect and supine heart rate but had no effect on systolic or diastolic blood pressure. Resting heart rate was lowest on the combination but this was not significantly different from that on atenolol. The combination reduced both erect and supine, systolic and diastolic, blood pressure.

All active treatments significantly reduced the heart rate during exercise. This was most pro-

Table 2 *Mean episodes of angina pectoris and glyceryl trinitrate consumption during each three week treatment period (excluding patient 10 (see text))*

			Treatment comparisons				
Variable	*F value*	*p value*	*Placebo*	*Verapamil*	*Atenolol*	*Combination*	*Pooled SE*
Angina pectoris	5·4	<0·005	23·6	15·2	17·7	7·1	2·9
Glyceryl trinitrate	5·7	<0·006	18·3	5·8	10·8	3·9	2·4

There is a significant difference between variables that are not connected by a line

Table 3 *Mean heart rate (HR), blood pressure (BP), and rate pressure product × 100 (RPP) at rest and at placebo run maximum exercise workload*

			Treatment comparisons				
Variable	*F value*	*p value*	*Placebo*	*Verapamil*	*Atenolol*	*Combination*	*Pooled SE*
Supine HR	44·0	<0·001	83	73	60	53	2·0
Standing HR	48·0	<0·0001	90	80	61	55	2·2
Maximum HR	66·0	<0·0001	121	107	91	77	2·4
Supine systolic BP	10·5	<0·001	136	139	138	122	2·5
Erect systolic BP	9·6	<0·001	137	131	125	115	3·0
Supine diastolic BP	9·7	<0·001	90	87	88	74	2·4
Erect diastolic BP	10·8	<0·001	91	83	82	71	2·5
Exercise systolic BP	14·9	<0·001	173	165	166	148	2·9
Resting RPP	39·0	<0·0001	113	102	83	65	3·6
Exercise RPP	51·0	<0·0001	215	178	153	116	6·3

There is a significant difference between variables that are not connected by a line.

Table 4 *Rest and exercise heart rate at maximum workload achieved during placebo run in*

	Resting heart rate				*Exercise heart rate*			
Patient	*P*	*V*	*A*	*C*	*P*	*V*	*A*	*C*
1	100	85	65	64	130	128	92	102
2	76	60	58	39	103	98	88	60
3	75	80	60	62	126	118	98	94
4	96	74	68	56	130	110	92	73
5	88	100	85	58	142	135	115	92
6	79	64	53	56	122	102	94	86
7	62	69	54	52	90	95	70	72
8	80	58	44	45	120	100	90	74
9	104	83	68	60	142	105	98	74
10	76	60	49	38	98	101	75	57
11	72	70	53	48	110	90	88	66

P, placebo; V, verapamil, A, atenolol; C, combination.

nounced on the combination, when the mean achieved heart rate was only 77 beats per minute—significantly lower than that on atenolol. Systolic blood pressure was lower during exercise only on the combination but the rise in blood pressure was similarly attenuated by all active treatments.

The rate pressure product was significantly reduced at rest and during exercise by all active treatments; the reduction was most marked on the combination.

16 point precordial electrocardiograpic mapping

During exercise 11, 6, 3, and 2 patients developed ST segment depression and 10, 8, 5, and 3 developed angina on placebo, atenolol, verapamil, and the combination respectively. The work done to the onset of angina pectoris was significantly increased only on verapamil and the combination ($p < 0.05$ and $p < 0.01$); work done to the onset of ST segment depression was significantly improved on all active phases ($p < 0.05$, $p < 0.005$, and $p < 0.001$ for atenolol, verapamil, and the combination respectively). On the combination seven patients showed no evidence of exercise induced ischaemia (ST depression or angina) compared with four on verapamil and one on atenolol.

Table 5 shows the area and sum of the ST segment depression immediately after exercise and during the 10 minute recovery period.

Twenty four hour ambulatory electrocardiographic monitoring

The figure shows the mean hourly heart rate during

Table 5 *Mean area of ischaemia (positive points) and ST segment depression at peak exercise and over the 10 minute recovery period as assessed by 16 point precordial electrocardiographic mapping*

			Treatment comparisons				
Variable	*F value*	*p value*	*Placebo*	*Verapamil*	*Atenolol*	*Combination*	*Pooled SE*
Peak exercise:							
Area of ischaemia	19·3	<0·001	5·2	0·7	2·3	0·4	0·5
ST depression	15·7	<0·001	7·1	0·9	2·7	0·6	0·8
Recovery:							
Area of ischaemia	14·3	<0·001	9·9	1·0	3·5	0·6	1·1
ST depression	13·0	<0·001	11·3	1·2	3·6	0·8	1·4

There is a significant difference between variables that are not connected by a line.

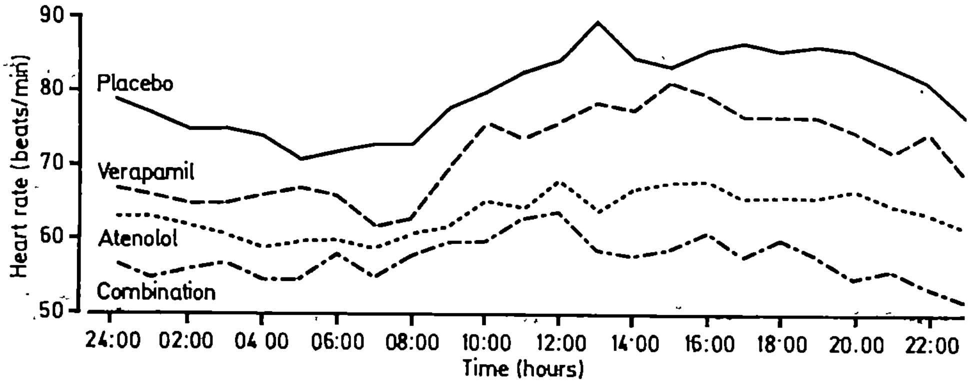

Figure *Mean hourly heart rate recorded during 24 hour ambulatory electrocardiographic monitoring.*

ambulatory monitoring. All active treatments reduced the heart rate. The combination produced the greatest reduction. The mean PR interval varied from 0·17 to 0·19 seconds and there was no difference between the active treatments; it exceeded 0·2 seconds in 1, 3, and 4 patients on atenolol, verapamil, and the combination respectively; only on verapamil did it exceed 0·22 seconds (0·26 and 0·28 in patients 6 and 4).

Radionuclide and ventriculography

The mean (pooled SE) resting left ventricular ejection fraction was similar on placebo, verapamil, and atenolol at 60, 57, and 59 but fell significantly on the combination to 53 (3). During exercise the mean (pooled SE) left ventricular ejection fraction did not change significantly and was similar at 55, 56, 57, and 53 (3) on placebo, verapamil, atenolol, and the combination respectively. On verapamil, atenolol, and the combination, 1, 1, and 4 patients respectively had a pronounced fall in left ventricular ejection fraction from placebo values (>10%). In only one patient was this associated with an adverse reaction.

Plasma concentrations of drugs and catecholamines

Plasma concentrations of both atenolol and verapamil varied greatly during single and combination treatments and there were no significant differences in mean concentrations between single and combination treatments. Mean concentrations of verapamil in μmol/l were 350 (range 127–600) and 445 (range 210–757), nor-verapamil 252 (range 77–376) and 324 (range 149–500), and atenolol 546 (range 130–1304) and 420 (range 100–867) on single and combination treatments respectively.

There was no consistent relation between verapamil and atenolol concentrations and subjective side effects or objective changes. Resting noradrenaline concentrations (normal range 0 8–3·0 nmol/l) were similar during all treatment periods: 2·48, 2·90, 2·81, and 2·36 (0·3) nmol/l (NS) for placebo, verapamil, atenolol, and the combination respectively.

SIDE EFFECTS

Adverse side effects were common during the combination treatment. Four patients (cases 12–15, table 1) withdrew from the study during the combination phase; one developed nodal rhythm, hypotension, and unstable angina requiring coronary artery vein graft surgery and three experienced severe dizziness and intolerable fatigue. These effects occurred within 24 hours of starting the combination treatment. The most serious adverse reaction that occurred in those completing the study was left ventricular failure occurring in association with a sinus bradycardia of 38 beats per minute together with frequent periods of sinus arrest, one of which lasted four seconds (patient 10). This resolved promptly with intravenous diuretics and an increase in heart rate occurred. He continued on the combination treatment with a diuretic. Radionuclide ventriculography was carried out three days later. Left ventricular ejection fraction was 43% compared with 47% on placebo. Patient 2 experienced persistent orthostatic dizziness, lethargy, and exertional dyspnoea. His standing blood pressure fell from 135/100 mm Hg to 112/75, 100/80, and 95/60 on placebo, verapamil, atenolol, and the combination respectively. On the combination he had a resting sinus bradycardia of 39 beats per minute which alternated with periods of nodal rhythm. In addition, there were episodes of sinus arrest with pauses of up to 2·5 seconds before nodal escape occurred. Three other patients experienced persistent fatigue or breathlessness (cases 4, 9, and 11). Although patients 9 and 11 had the lowest resting ejection fraction on placebo (46% and 47% respectively), only patient 2 had a considerable fall in resting ejection fraction on the combination (from 64% to 49%).

During ambulatory monitoring patient 9 showed similar but less frequent episodes of bradycardia as patient 2. Patient 11 developed considerable ankle oedema during combination treatment but there was no other clinical evidence of heart failure. Patient 8 demonstrated sinus bradycardia on atenolol alone; the lowest recorded rate being 38 beats per minute for five seconds.

No important problems were encountered during placebo or verapamil treatment. Constipation was troublesome in two patients on verapamil and on the combination; and another patient was constipated on atenolol. Five patients expressed a preference for verapamil as the most effective and acceptable treatment, one for atenolol, two for the combination, and three had no preference.

Discussion

Despite earlier equivocal studies verapamil in doses of 360 to 480 mg per day is an effective antianginal agent.[16–18] In this study verapamil markedly reduced exercise induced ischaemia and was at least as effective as atenolol despite producing a smaller reduction in the exercise rate pressure product. Similar observations were reported when verapamil was compared with propranolol[17–19] and these support the view that verapamil may have additional properties, including favourable effects on coronary blood flow and ventricular diastolic function.[20]

Verapamil produced greater mean reductions in all objective and subjective indices of ischaemia than did atenolol but in general the combination was the most effective treatment. Although the reduction in the frequency of angina and in glyceryl trinitrate consumption was greatest during combination treatment, almost 50% of patients found that verapamil was the most acceptable treatment.

On combination treatment there was a pronounced reduction in the rate pressure product during exercise, principally through a lowering of heart rate, which was significantly greater than that on atenolol alone. Though reduction in exercise tachycardia is an important factor in lowering myocardial oxygen consumption, the considerable fall in heart rate that occurred in some of our patients may not be entirely beneficial. It may lead to such a reduction in cardiac output that lethargy and fatigue will occur during even moderate exertion and it is possible that the subjective side effects observed resulted from this effect.

The negative inotropic and chronotropic effects of short term verapamil treatment are offset by the reflex increase in sympathetic activity consequent upon the fall in systemic vascular resistance.[21] When verapamil is given for longer increased sympathetic activity is unlikely to persist.[22] In this study concentrations of plasma noradrenaline were similar (and normal) during all four treatment periods.

Resting left ventricular ejection fraction did not change on either of the active mono treatments, and though a significant fall has been reported on verapamil alone[20] our findings resemble those of other investigators.[3 9 17 18] On the combination treatment, however, mean left ventricular ejection fraction fell significantly and left ventricular failure developed in one patient. The increase in heart size and the development of dyspnoea and cardiac failure noted in other studies[1 8 9] emphasise the potential of the combination of verapamil and a β blocker to depress myocardial contractility.

The left ventricular ejection fraction did not rise normally during exercise on any active treatment, despite the pronounced improvement in other indices of ischaemia. This accords with other studies of verapamil and has also been reported with propranolol.[3 9 18] None the less, in a previous study comparing nifedipine and atenolol, singly and in combination, left ventricular ejection fraction rose during exercise on nifedipine and on the combination but not on atenolol.[5] This does not necessarily imply that this combination exerts a greater anti-ischaemia effect; rather it suggests that a greater reduction in left ventricular afterload occurs with nifedipine which is the most potent vasodilator among the existing calcium antagonists.

We observed a wide inter- and intraindividual variation in plasma concentrations of verapamil, with a range which resembled that reported in other studies.[8 17 18 23] The probable lower effective plasma concentration of verapamil is around approximately 100 μmol/l; in general plasma concentrations of verapamil above this bear little relation to the clinical effect.[24] Verapamil undergoes rapid and extensive first pass metabolism,[25] as do the lipophilic β blockers such as propranolol, oxprenolol, and metoprolol.[26] A pharmacokinetic interaction has been described between metoprolol and verapamil[27] though Warrington *et al* did not demonstrate such an interaction between verapamil (50 mg three times a day) and propranolol, metoprolol, or atenolol.[28] We postulated that atenolol, an hydrophilic cardioselective β blocker that does not undergo appreciable hepatic metabolism and is excreted largely unchanged by the kidneys,[26] would not be susceptible to such an interaction with verapamil. To our knowledge there are no reported data on the long term influence of β blockade on verapamil concentrations in patients with coronary heart disease. We observed a modest rise in mean plasma concentrations of verapamil and nor-verapamil during combination treatment, which was not statistically significant.

Plasma concentrations of verapamil and atenolol taken from patient 10 during his admission with cardiac failure (12 hours post-dose) were 448 and 276 μmol/l respectively. Two days later (2 and 6 hours post-dosing), when the cardiac failure had resolved, the concentrations were 210 and 100 μmol/l respectively, the lowest recorded in any patient. It may be that relief of hepatic congestion and increased renal perfusion improved metabolism and excretion and thus produced lower concentrations of these agents. In general, however, there was no obvious relation between plasma concentrations and observed and reported adverse reactions. It would be difficult to demonstrate such a relation, given the reported wide variability of plasma concentrations within individuals even over a 24 hour period.[29 30] Plasma concentrations in this study varied considerably during single and combination treatment. The absence of a consistent change during combination treatment does not suggest an important pharmacokinetic interaction; thus we conclude that the effects of this combination are principally the result of pharmacodynamic interaction.

Previously the safety and efficacy of combining verapamil with a β blocker have been studied mainly with propranolol[1 8 9 23 31] but major adverse effects have been reported during combination with other β blockers.[32 33] The reported frequency of haemodynamic and electrophysiological adverse reactions is variable; and in one review it was reported to be approximately 14%.[34] These results were obtained in selected patients who had previously tolerated both types of drug,[1 31] and in whom the dose was titrated to avoid adverse effects,[1 8] and who had been studied in a previous trial[1] or under hospital supervision.[8 9 23 31] Furthermore, in patients with poor effort capacity and depressed ventricular ejection fraction the frequency of adverse reactions rises significantly.[31]

Reports of the combination of verapamil and atenolol in patients with angina pectoris are sparse. In one study adverse reactions were not reported[35] and in another open study mild left ventricular failure occurred in five of 31 patients in whom verapamil was added to atenolol to control resistant angina.[36] In contrast, we experienced quite frequent (and in one case severe) adverse reactions on the combination that were not readily predictable even with detailed knowledge of cardiac function. Despite a fall in mean left ventricular ejection fraction on the combination, these side effects occurred principally in those in whom important bradycardia occurred.

Thus in this study we have used these two drugs at doses that might be considered maximal. Both are effective antianginal agents and it is likely that they will be used in combination in patients with angina. If they are we advise that the dose of the drug currently being taken should be reduced when a low dose of the other drug is added, and that the doses should be titrated to achieve the maximum tolerated effective dose. The presence of a previous myocardial infarction should alert the clinician to the possibility that the patient may tolerate combination treatment poorly. Any documented bradycardia is an absolute contraindication to such treatment.

CONCLUSION

Verapamil was an effective and well tolerated alternative to atenolol in patients whose exercise capacity was severely limited by chest pain. Since most patients were incompletely controlled on β blockers before entry into the study, a selection bias against atenolol may have been a factor. The data do suggest, however, that it would be appropriate to change from a β blocker to verapamil if the patient's symptoms are not controlled, before adding another antianginal agent. The combination of these agents further improved overall effectiveness; it has a place in certain patients but caution is required in its use, which must be closely supervised.

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Appendix

(a) The presentation of results gives an F value and corresponding p value of the test of the hypothesis that all four treatments give the same average response for that variable.

(b) The treatment comparisons P, placebo; V, verapamil; A, atenolol; and C, combination are given in a standard form to be interpreted as follows.

(i) $\overline{\mathrm{P}}\ \overline{\mathrm{V}}\ \overline{\mathrm{A\ C}}$ means that there is no significant difference between the treatments C and A but both are different from V and also from P which itself is different from V.

(ii) $\overline{\mathrm{P\ V\ A}}\ \overline{\mathrm{C}}$ means that the only significant differences were between C and each of the three treatments which themselves showed no significant differences between themselves.

(iii) $\overline{\mathrm{P\ V\ }\overline{\mathrm{A}}}\overline{\mathrm{\ C}}$ means that C and A were not significantly different and that no separation between A, V, and P could be found—that is the only significant differences were between C and V and between C and P.

Virtually all F tests were referred to a $F^{3\ 30}$ distribution. The pooled standard error (SE) of the mean for any variable is given after the mean values.

References

1 Leon MB, Rosing DR, Bonow RO, Lipson LC, Epstein SE Clinical efficacy of verapamil alone and combined with propranolol in treating patients with chronic stable angina pectoris. *Am J Cardiol* 1981,48:131–9.

2 Dargie HJ, Lynch PG, Krikler DM, Harris L, Krikler S Nifedipine and propranolol· a beneficial drug interaction. *Am J Med* 1981;71 676–82.

3 Johnson SM, Mauritson DR, Corbett JR, Woodward W, Willerson JT, Hillis LD Double blind, randomised, placebo-controlled comparison of propranolol and verapamil in the treatment of patients with stable angina pectoris. *Am J Med* 1981,71·443–51

4 Opie LH Calcium antagonists. Mechanisms, therapeutic indications and reservations. *Q J Med* 1984;53 1–16.

5 Findlay IN, MacLeod K, Ford M, Gillen G, Elliott AT, Dargie HJ. Treatment of angina pectoris with nifedipine and atenolol efficacy and effect on cardiac function. *Br Heart J* 1986;55:240–5.

6 Tweddel AC, Beattie JM, Murray RG, Hutton I. The combination of nifedipine and propranolol in the management of angina pectoris. *Br J Clin Pharmacol* 1981,12:229–33.

7 Rowland E, Razis P, Sugrue D, Krikler DM. Acute and chronic haemodynamic and electrophysiological effects of nifedipine in patients receiving atenolol. *Br Heart J* 1983;50:383–9.

8 Winniford MD, Huxley RL, Hillis LD Randomised, double blind comparison of propranolol alone and a propranolol-verapamil combination in patients with severe angina of effort *J Am Coll Cardiol* 1983;1:492–8

9 Johnstone DL, Gebhardt VA, Donald A, Kostuk WJ. Com-

parative effects of propranolol and verapamil alone and in combination on left ventricular function and volumes in patients with chronic exertional angina: a double blind, placebo controlled, randomised cross over study with radionuclide ventriculography *Circulation* 1983;68.1280–9.

10 Fox K, Selwyn A, Shillingford J. Precordial electrocardiograph mapping after exercise in the diagnosis of coronary artery disease. *Am J Cardiol* 1979,43:541–6.

11 Bhamra RK, Thorley KJ, Vale JA, Holt DW. High performance liquid chromatographic measurement of atenolol· methodology and clinical applications. *Ther Drug Monit* 1983,5.313–8.

12 Cole SC, Flanagan RJ, Johnston A, Holt DW Rapid high performance liquid chromatographic method for the measurement of verapamil and nor-verapamil in blood plasma or serum. *J Chromatogr* 1981,218:621–9.

13 Ball SG, Tree M, Morton JJ, Inglis GC, Fraser R. Circulating dopamine: its effect on the plasma concentrations of catecholamines, renin, angiotensin, aldosterone and vasopressin in the conscious dog. *Clin Sci* 1981,61.417–22.

14 Wallenstein S, Zucker CL. Fleiss JL. Some statistical methods useful in circulation research. *Circ Res* 1980;47.1–9.

15 Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient II Analysis and examples. *Br J Cancer* 1977,35.1–39.

16 Bala Subramanian V, Paramasivan R, Lahiri A, Raftery EB Verapamil in chronic stable angina: a controlled study with computerised multistage treadmill exercise. *Lancet* 1980;i·841–4.

17 Sadick NN, Tan ATH, Fletcher PJ, Morris J, Kelly DT. A double blind randomised trial of propranolol and verapamil in the treatment of effort angina. *Circulation* 1982;66:574–9.

18 Josephson MA, Hecht HS, Hopkins J, Guerrero J, Singh BM: Comparative effects of oral verapamil and propranolol on exercise induced myocardial ischaemia and energetics in patients with coronary artery disease. single blind placebo crossover evalution using radionuclide ventriculography. *Am Heart J* 1982;103:978–85.

19 Arnman K, Ryden L. Comparison of metoprolol and verapamil in the treatment of angina pectoris. *Am J Cardiol* 1982;49:821–7.

20 Bonow RO, Leon MB, Rosing DR, *et al.* Effects of verapamil and propranolol on left ventricular systolic and diastolic filling in patients with coronary artery disease: radionuclide angiographic studies at rest and during exercise *Circulation* 1982,65 1337–50

21 Singh BN, Chew CYC, Josephson MA, Packer M. Pharmacologic and hemodynamic mechanisms underlying the antianginal actions of verapamil. *Am J Cardiol* 1982;50:886–93.

22 Laederach K, Gerber A, Weidmann P. Effect of calcium antagonists on blood pressure, catecholamines, renin, aldosterone and cardiovascular pressor responsiveness in normal and hypertensive man. In: Althaus U, Burckhardt D, Vogt E, eds. *Calcium-antagonismus/international symposium on calcium antagonism.* Frankfurt/Main. Universimed. Verlag, 1984: 93–115.

23 Winniford MD, Fulton KL, Corbett JR, Croft CH, Hillis LD Propranolol-verapamil versus propranolol-nifedipine in severe angina pectoris of effort: a randomised, double blind, crossover study. *Am J Cardiol* 1985;55.281–5.

24 Frishman W, Kirsten E, Klem M, *et al.* Clinical relevance of verapamil plasma levels in stable angina pectoris. *Am J Cardiol* 1982;50:1180–4.

25 Hendry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. *Am J Cardiol* 1980,46:1047–58.

26 Cruikshank JM. The clinical importance of cardioselectivity and lipophilicity in beta blockers *Am Heart J* 1980, 100:160–78.

27 McLean AJ, Knight R, Harrison PM, Harper RW. Clearance based oral drugs interaction between verapamil and metoprolol and comparison with atenolol *Am J Cardiol* 1985;55 1628–9.

28 Warrington SJ, Holt D, Johnston A, Fitzsimons TJ. Pharmacokinetics and pharmacodynamics of verapamil in combination with atenolol, metoprolol and propranolol. *Br J Clin Pharmacol* 1984;17.37S–44S.

29 Eichelbaum M, Somogyi A. Verapamil distribution in health and the diseased state In. Althaus U, Burckhardt D, Vogt E, eds. *Calcium-antagonismus/international symposium on calcium antagonism.* Frankfurt/Main. Universimed Verlag, 1984:64–71.

30 Eichelbaum M. Clinical pharmacology of the calcium channel blockers. In. Lemberger L, Reidenberg MM, eds. *Proceedings of the second world conference on clinical pharmacology and therapeutics.* Bethesda, Maryland. American Society for Pharmacology and Experimental Therapeutics, 1984.774–87.

31 Subramanian B, Bowles MJ, Davies AB, Raftery EB. Combined therapy with verapamil and propranolol in angina pectoris. *Am J Cardiol* 1982;49 125–32.

32 Wayne VS, Harper RW, Laufer E, Federman J, Anderson ST, Pitt A. Adverse interaction between beta adrenergic blocking drugs and verapamil—report of three cases. *Aust NZ J Med* 1982;12:285–9.

33 Hutchison SJ, Lorimer AR, Lakhdar A, McAlpine SG. Beta blockers and verapamil. a cautionary tale. *Br Med J* 1984,289·659–60.

34 Leon MB, Rosing DR, Bonow RO, Epstein SE. Combination therapy with calcium-channel blockers and beta blockers for chronic stable angina pectoris *Am J Cardiol* 1985; 55.69B–80B.

35 Lessem J. Combined therapy with Ca-antagonists and beta-adrenergic combinations in chronic stable angina. *Acta Med Scand* 1982; suppl 681:83–90.

36 McGourty JC, Silas JH, Solomon SA. Tolerability of combined treatment with verapamil and beta blockers in angina resistant to monotherapy. *Postgrad Med J* 1985,61·229–32.

Br Heart J 1987;57:344–7

Left main coronary artery occlusion with preserved left ventricular function: a report of three cases

ANDREW H WATT,[*] WILLIAM J PENNY,[†] MICHAEL S T RUTTLEY[‡]

*From the Departments of *Pharmacology and Therapeutics, †Cardiology, and ‡Radiology, University of Wales College of Medicine, Heath Park, Cardiff*

SUMMARY Three patients with angina pectoris are reported in whom occlusion of the left main coronary artery was found at coronary arteriography. In these three patients left ventricular function was well preserved. In all three the right coronary artery was dominant and there were prominent epicardial and septal collateral vessels to the territories normally supplied by the left anterior descending and circumflex arteries.

It seems reasonable to suggest that this coronary artery anatomy and collateral vessel formation accounted for the preservation of the left ventricular myocardium in these patients.

It has recently been proposed that occlusion of a coronary artery is commonly precipitated by rupture of an atherosclerotic plaque followed by superimposed thrombosis.[1] The reduction of local blood flow to the myocardium commonly results in segmental myocardial infarction or sudden death. The extent of the area of infarcted myocardium depends in part on the degree of availability of alternative sources of blood supply. Two mechanisms of alternative blood supply that may be important in reducing the volume of infarcted myocardium are variations in the size and distribution of the coronary arteries and the development of collateral vessels. The degree of development of collaterals may depend on the duration of angina pectoris and the frequency and severity of episodes of myocardial ischaemia; but the time course for development of collateral vessels in man is not known.[2]

We report three patients with angina pectoris in whom occlusion of the left main coronary artery was found at coronary arteriography but in whom little or no impairment of left ventricular function was detectable. The possible contribution of variations in coronary anatomy and of collateral vessel formation to preservation of left ventricular function in such patients is discussed.

Patients and methods

CASE 1

This 60 year old man presented with a two month history of angina pectoris precipitated by exertion. The clinical impression of angina pectoris was confirmed by a positive exercise test. Physical examination was normal. Symptomatic improvement occurred initially on medical treatment, but he continued to experience angina and cardiac catheterisation was performed two years after presentation.

At cardiac catheterisation the left ventricular angiogram was normal; the ejection fraction was 60%. The left ventricular end diastolic pressure was raised, being 15 mm Hg before angiography and rising to 23 mm Hg. The main stem of the left coronary artery was occluded. The right coronary artery was dominant; however, the posterior descending artery did not reach the cardiac apex. A large collateral channel between the acute marginal branch of the right coronary artery and the left anterior descending artery was displayed. It had a calibre equal to that of the right ventricular wall branch and distal left anterior descending artery. Smaller collateral vessels connected the posterior descending artery to the distal left anterior descending artery, the conus artery to the proximal left anterior descending artery, the sinoatrial node artery to the left atrial circumflex, and the distal right coronary artery to the distal circumflex artery. There was extensive collateral development in the inter-

Requests for reprints to Dr Andrew H Watt, Department of Pharmacology and Therapeutics, University of Wales College of Medicine, Heath Park, Cardiff CF4 4XN

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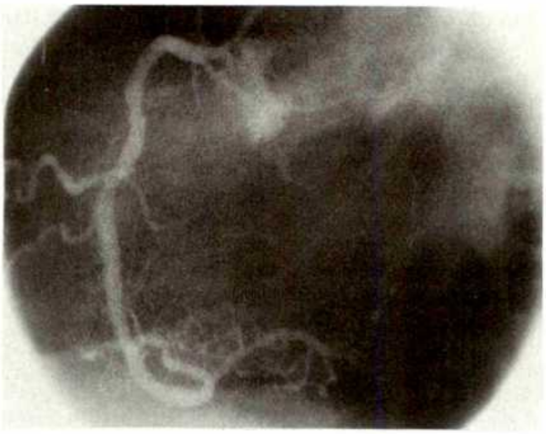

Fig 1 *Angiogram (left anterior oblique projection) obtained after injection of contrast into the right coronary artery in patient 1.*

ventricular septum. There was a minor proximal right coronary artery stenosis with further lesions in the left anterior descending and circumflex arteries, which filled from the right coronary artery injection via the collateral channels described above (figs 1 and 2).

The patient steadfastly declined operation. Two years after cardiac catheterisation he continued to have stable effort angina pectoris, which he considered to be adequately controlled by medical treatment.

CASE 2

A 60 year old man was referred with a 16 month history of typical exertional angina of increasing severity despite medical treatment. Physical examination was unremarkable. An exercise test was positive.

At cardiac catheterisation slight apical hypokinesia was noted on the left ventricular angiogram. The ejection fraction was 50%. The left ventricular

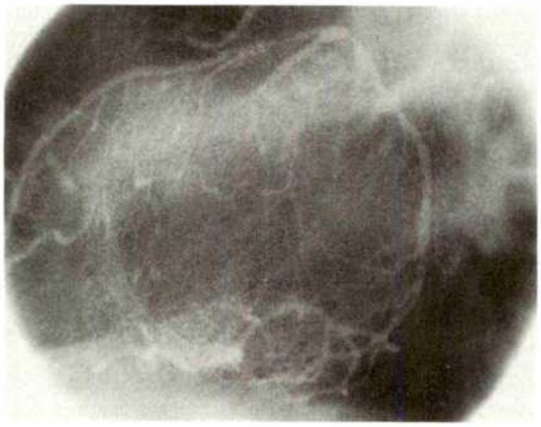

Fig 2 *Angiogram obtained in the late phase of the right coronary artery injection shown in fig 1, demonstrating filling of the left anterior descending and circumflex coronary arteries and extensive development of collateral vessels.*

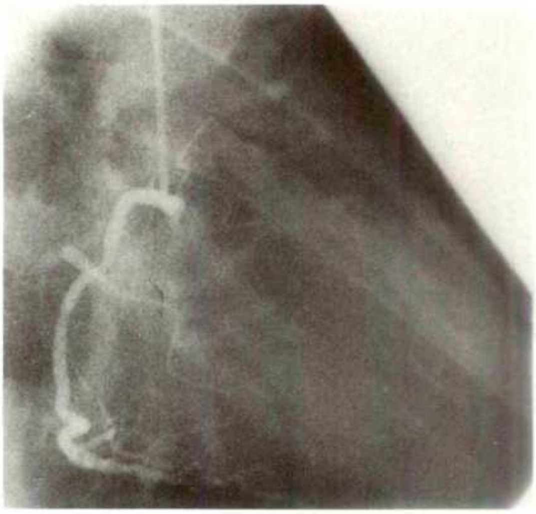

Fig 3 *Angiogram (right anterior oblique projection) obtained after injection of contrast into the right coronary artery in patient 2.*

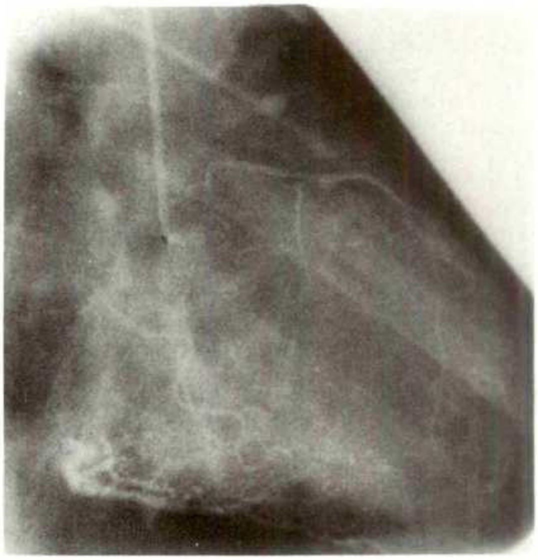

Fig 4 *Angiogram of the late phase of the right coronary artery injection shown in fig 3, demonstrating filling of the left anterior descending coronary artery.*

end diastolic pressure was 10 mm Hg before the angiogram and 11 mm Hg after it. The main stem of the left coronary artery was occluded. The dominant right coronary artery had a 40% proximal stenosis and had one large and two small left ventricular wall branches, and the posterior descending artery reached the cardiac apex. The left anterior descending artery was short and did not reach the cardiac apex. There was considerable development of epicardial and septal collateral channels. Stenoses were noted in the left anterior descending artery and circumflex arteries, which filled from the right coronary artery injection (figs 3 and 4).

This patient was referred for coronary artery surgery. Vein grafts were placed in the left anterior descending artery and one of its diagonal branches, the obtuse marginal branch of the circumflex, and in the posterior descending branch of the right coronary artery. Six months after operation he was well and symptom free.

CASE 3

A 49 year old man presented with a one year history of angina precipitated by cold or exertion. He had hypertension controlled by medical treatment. Physical examination was normal. The electrocardiogram showed left ventricular hypertrophy (SV1 + RV5 = 37 mm) and T wave inversion in leads I, aVL, and V2 – V6. Echocardiography confirmed mild concentric left ventricular hypertrophy.

At angiography the left ventricular angiogram was normal; the ejection fraction was 71%. Left ventricular end diastolic pressure was 10 mm Hg before the angiogram and 15 mm Hg after it. The main stem of the left coronary artery was occluded. The right coronary artery was dominant with a 30% proximal stenosis and two large left ventricular wall branches extending beyond the posterior descending artery. Both the posterior descending artery and left anterior descending artery reached the cardiac apex. A large collateral channel joined the right coronary artery conus to the left anterior descending conus branches, and numerous smaller collateral channels were also seen. The distal left anterior descending and circumflex arteries filled from the right coronary artery injection.

The patient was referred for coronary artery surgery. Vein grafts were inserted into the left anterior descending, diagonal, ramus medianus, and posterior descending arteries. Three months after operation he was symptom free.

Discussion

Occlusion of the left main coronary artery may be associated with sudden death and with widespread myocardial infarction leading to cardiogenic shock and death or continuing severe disability. In contrast, the patients with left main coronary artery occlusion who we describe all had normal left ventricular ejection fractions and in only one patient was a minor focal abnormality of left ventricular contraction discernible on the left ventricular angiogram.

Preserved ventricular function when the left main coronary artery is occluded implies that the myocardium that is normally supplied by the left coronary artery receives a supply of oxygen and metabolic substrates from the right coronary artery that is adequate to maintain myocardial contractile function. In each of our three patients the right coronary artery was dominant and there were prominent epicardial and septal collateral vessels to the territories normally supplied by the left anterior descending and circumflex arteries. In patient 1 a large right ventricular wall branch of the right coronary artery was virtually continuous with the left anterior descending artery through a large collateral vessel.

It would seem reasonable to suggest that the basis for survival of the left ventricular myocardium in these patients depends on the presence of the dominant right coronary artery and development of epicardial and septal collateral vessels to supply distal branches of the left coronary artery.

We are aware of only one previous report of left main coronary artery occlusion with preserved left ventricular function.[3] These workers did not comment on the possible benefit of right coronary artery dominance in this context but the right coronary artery in one patient was said to be large. In two of their patients the ejection fraction was normal, and in three patients who were comparable with ours left ventricular end diastolic pressure was considerably increased (22–23 mm Hg), whereas in only one of our three patients was left ventricular end diastolic pressure raised to the same extent. Though they commented on the existence and functional importance of right coronary artery to left coronary artery collaterals in their patients, Frye *et al* gave no details of collateral development.[3] In the cases from both series the importance of intercoronary collaterals is convincing whereas the functional importance of coronary collaterals more generally is less certain.[2]

Haemodynamically important stenosis of the left main coronary artery in association with angina pectoris is an important indication for coronary artery bypass grafting[4]; such surgical intervention has been shown to improve symptoms and life expectancy. The place of operation in the management of patients with left main coronary artery occlusion is less well defined. Patient 2 had a 40% proximal stenosis of the right coronary artery, which may reasonably be considered to be at least as important as a stenosis of the left main coronary artery, because not only are the left anterior descending and circumflex territories at risk if the vessel becomes occluded but also the right coronary artery territory. Patient 3 also had a minor stenosis of the right coronary artery, with similar implications in terms of the myocardium at risk. Thus in these patients coronary artery bypass grafting was carried out. Patient 1 had only trivial disease in the right coronary artery, and so the indications for operation were less clear cut than in the other two patients; but as the entire ventricular myocardium depended on continued patency of one vessel (the right coronary artery) coronary artery surgery was recommended. The patient refused this and two years after identification of the left main coronary artery occlusion, he continues to have stable effort angina. A similar patient reported by Frye *et al* also declined operation and had stable effort angina 2·5 years after angiography.[3] Perhaps left main coronary artery occlusion with a normal right coronary artery carries a less adverse prognosis than left main coronary artery stenosis, and there may be consequent implications for surgical management; but at present too few data are available for firm conclusions to be drawn.

References

1 Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. *Br Heart J* 1985;53:363–73.

2 Alpert JS, Braunwald E. Acute myocardial infarction: pathological, pathophysiological and clinical manifestations. In: Braunwald E, ed. *Heart disease. A textbook of cardiovascular medicine.* 2nd ed. Philadelphia: WB Saunders, 1984:1262–300.

3 Frye RL, Gura GM, Chesebro JH, Ritman EL. Complete occlusion of the left main coronary artery and the importance of coronary collateral circulation. *Mayo Clin Proc* 1977;52:742–5.

4 Takaro T, Hultgren HN, Lipton MJ, *et al.* The VA cooperative randomised study of surgery for coronary arterial occlusive disease. II Subgroup with significant left main lesions. *Circulation* 1976; **54**(suppl 3):107–17.

Br Heart J 1987;57:348–55

A comparison of the assessment of mitral valve area by continuous wave Doppler and by cross sectional echocardiography

FRANCESCO LOPERFIDO, FRANCESCO LAURENZI, FABRIZIO GIMIGLIANO, FAUSTINO PENNESTRI', LUIGI M BIASUCCI, CARLO VIGNA, FRANCESCO DE SANTIS, ANGELA FAVUZZI, ELISABETTA ROSSI, UGO MANZOLI

From the Department of Cardiology, Catholic University of Sacro Cuore, Rome, Italy

SUMMARY Transmitral pressure half time (PHT) was assessed by continuous wave Doppler in 44 patients with rheumatic mitral valve stenosis (14, pure mitral valve stenosis; 15, combined mitral stenosis and regurgitation; and 15 with associated aortic valve regurgitation). The mitral valve area, derived from transmitral pressure half time by the formula 220/pressure half time, was compared with that estimated by cross sectional echocardiograpy. The transmitral pressure half time correlated well with the mitral valve area estimated by cross sectional echocardiography. The correlation between pressure half time and the cross sectional echocardiographic mitral valve area was also good for patients with pure mitral stenosis and for those with associated mitral or aortic regurgitation. The regression coefficients in the three groups of patients were significantly different. Nevertheless, a transmitral pressure half time of 175 ms correctly identified 20 of 21 patients with cross sectional echocardiographic mitral valve areas $<1{\cdot}5$ cm^2. There were no false positives. The Doppler formula significantly underestimated the mitral valve area determined by cross sectional echocardiography by 28 (9)% in 19 patients with an echocardiographic area >2 cm^2 and by 14·8 (8)% in 25 patients with area of <2 cm^2. In thirteen patients with pure mitral valve stenosis Gorlin's formula was used to calculate the mitral valve area. This was overestimated by cross sectional echocardiography by 0·16 (0·19) cm^2 and underestimated by Doppler by 0·13 (0·12) cm^2. Continuous wave Doppler underestimated the echocardiographic mitral valve area in patients with mild mitral stenosis. The Doppler formula mitral valve area = 220/pressure half time was more accurate in predicting functional (haemodynamic) than anatomical (echocardiographic) mitral valve area.

Cross sectional echocardiography gives an accurate estimate of mitral valve area.[1] When echocardiographic images are unsatisfactory,[1-8] Doppler echocardiography is an alternative method of assessing the mitral valve area.[9-16] The Doppler estimate of mitral valve area correlated well with the results of catheterisation even when there was mitral regurgitation or low cardiac output.[13 16 17] The results of heart catheterisation may not be the "gold standard" for mitral valve area assessment because coexistent mitral regurgitation will lead to inaccuracy.[18-20] Even in patients with pure mitral stenosis, catheterisation is probably less accurate than cross sectional echocardiography in predicting the anatomical mitral valve orifice.[1]

There are only a few studies in which Doppler and cross sectional echocardiographic estimates of mitral valve area were compared,[21 22] and the influence of mitral regurgitation was not specifically considered.[22] We investigated the value of transmitral pressure half time, determined by continuous wave Doppler,[9 10 13 16 17] in predicting the echocardiographic mitral valve area in patients with

Requests for reprints to Dr Francesco Loperfido, Istituto di Cardiologia, Università' Cattolica S Cuore, Policlinico A Gemelli, L go Gemelli 8, 00168 Rome, Italy

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mitral stenosis. We also examined the influence of associated mitral or aortic regurgitation on this comparison.

Patients and methods

PATIENTS

From June 1984 to the end of January 1985, 52 consecutive patients with rheumatic mitral stenosis were examined by cross sectional echocardiography and continuous and pulsed wave Doppler. Patients in whom cross sectional echocardiography showed thickened mitral leaflets, abnormal diastolic motion of the mitral leaflet, and a mitral valve area of <3 cm^2 [1] were considered for subsequent analysis. Patients with previous mitral valvotomy, aortic valve stenosis, or a history of arterial hypertension were excluded. Nine patients were excluded because of inadequate echocardiographic studies and three because Doppler studies were unsatisfactory. Thus we studied 44 patients (38 women and 6 men) aged 24 to 77 years (mean 46 (12)). At the time of investigation 28 patients were in sinus rhythm and 16 in atrial fibrillation. We subdivided the patients into three groups on the basis of Doppler and heart catheterisation findings (when available): group 1 had pure mitral stenosis; group 2 had mitral stenosis and regurgitation; and group 3 had mitral stenosis (with or without mitral valve regurgitation) and aortic regurgitation.

CROSS SECTIONAL ECHOCARDIOGRAPHIC AND DOPPLER METHODS

Cross sectional echocardiographic and Doppler studies were performed by means of a real time phased-array system (Toshiba SSH-40A) connected to a Doppler unit (Toshiba SS-21B). Transducers with a frequency of 2·4 and 3·5 MHz were used for imaging and pulsed wave Doppler and 2·4 MHz for continuous wave Doppler.

Cross sectional echocardiography was performed by the standard technique. We assessed the mitral valve area from the parasternal short axis view, taking care to image the orifice from a transducer location that was perpendicular to the valve at the level of its maximal narrowing and at optimal gain settings.[1] Mitral valve area was automatically calculated on the video screen by use of a built-in system of movable electronic callipers on the stop frame that showed mitral valve opening in early ventricular diastole. The inner margin of the orifice was traced.[2 4 5]

Transmitral flow was examined by continuous wave Doppler from the apex with the patient in the left lateral decubitus position.[1 7] The Doppler signal reproduced as an audio signal and the spectral analysis of frequencies was obtained in real time by fast Fourier transform. The maximum measurable frequency for continuous wave Doppler was 12 kHz. In all studies the cutoff frequency of the filter was 400 Hz. Care was taken to obtain spectral patterns with an uninterrupted high frequency profile.[13 23] Velocity profiles were recorded at a speed of 50 mm/s on a Sony videotape recorder. Hard copies for subsequent analysis were reproduced with a strip chart recorder. In each study the incident Doppler beam was kept nearly perpendicular to mitral valve plane by means of intermittent cross sectional echocardiographic imaging. We did not correct for the Doppler flow angle.

We calculated the transmitral peak pressure drop (ΔP) by measuring the maximal velocity (V) in early diastole and by use of the equation: $\Delta P = 4V^2$. The transmitral mean pressure drop was calculated from the curve that we obtained by calculating the pressure drop for several points during diastole.[13] We measured velocity at the upper limit of the frequency

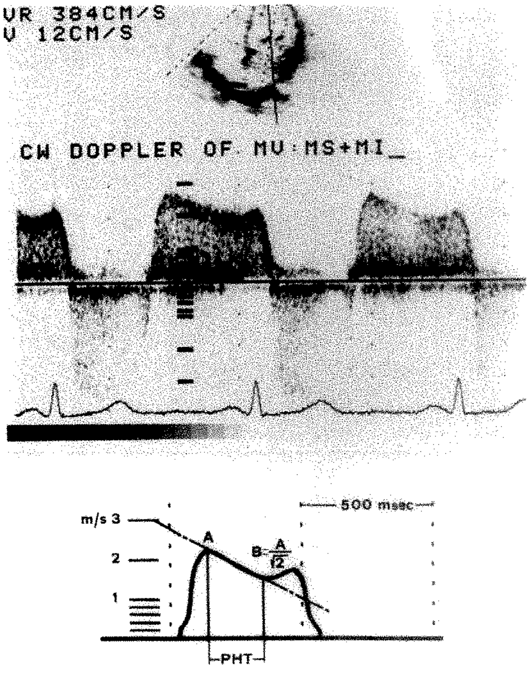

Fig 1 *(Top) Transmitral flow velocity curve obtained by continuous wave Doppler from the apical approach. (The solid line within the echocardiographic image is the Doppler beam.) (Middle) Flow velocity profile; flow below the zero line in systole indicates mitral regurgitation. The first 5 bars above and below the zero line represent calibration of 0·2 m/s and the next bars represent 1 m/s. (Bottom) Method for obtaining transmitral pressure half time(PHT). A, peak velocity; B, half peak pressure.*

profile. Peak and mean pressure drop were expressed as mm Hg. Atrioventricular pressure half time was obtained by dividing the peak velocity by 1·4 and by measuring the time from the peak velocity to the point at which this decrease in velocity was found (fig 1).[17] Data were rounded to 5 ms. Peak and mean pressure drops and pressure half time were measured as the mean of 10 consecutive cardiac cycles either in sinus rhythm or atrial fibrillation.[13]

Mitral and aortic regurgitation were assessed by pulsed wave Doppler.[24–28] Mitral regurgitation was identified in apical four chamber and parasternal long axis views when a high-pitched, whistling audio signal was present within the left atrium for at least one third of systole.[20–23] When a mitral regurgitant flow was audible we used a cross sectional echocardiographic image of the left atrial area to obtain a semiquantitative assessment of regurgitant flow distribution. Mitral regurgitation was graded as: 1+, turbulence just behind mitral valve; 2+, extension of turbulence to the inferior half of left atrium; and 3+, turbulence spreading even further.[24] Aortic regurgitation was identified in apical right anterior oblique (or equivalent) and parasternal long axis views when there was diastolic turbulence within the left ventricle. It was differentiated from mitral stenosis flow by: (*a*) locating the sample volume immediately under the aortic leaflets; (*b*) accurately timing the onset of turbulence before mitral valve opening by simultaneous M mode echocardiographic recording.[24–26] A distribution of Doppler frequencies that was typical of the aortic regurgitation, in which a

Table *Cross sectional echocardiographic, continuous wave Doppler echocardiographic, and heart catheterisation data in 44 patients with rheumatic mitral valve stenosis*

	Cross sectional		*Doppler*			*Catheterisation*			
Patient No	*MVA (cm²)*	*Peak gradient (mm Hg)*	*Mean gradient (mm Hg)*	*PHT (ms)*	*MVA (cm²)*	*Mean gradient (mm Hg)*	*MVA (cm²)*	*MR*	*AR*
1	0·8	13	9	260	0·8	8	1·0	—	—
2	0·9	14	8	265	0·8	10	0·7	—	—
3	1·0	19	17	210	1·0	NA	NA	—	—
4	1·1	27	16	245	0·9	16	1·0	—	—
5	1·3	9	7	220	1·0	8	1·4	—	—
6	1·3	14	12	220	1·0	9	1·2	—	—
7	1·4	21	15	200	1·1	10	1·2	—	—
8	1·4	9	5	190	1·2	6	1·3	—	—
9	1·6	8	5	155	1·4	6	1·6	—	—
10	2·0	7	6	150	1·5	4	1·7	—	—
11	2·0	9	7	140	1·6	8	1·7	—	—
12	2·1	15	8	135	1·6	5	1·6	—	—
13	2·2	8	6	120	1·8	7	1·9	—	—
14	2·4	13	8	110	2·0	4	2·1	—	—
15	0·9	23	21	240	0·9	17	NA	+	—
16	1·0	21	14	210	1·0	16	NA	+	+ + +
17	1·1	14	9	250	0·9	13	NA	—	+ +
18	1·1	38	12	220	1·0	15	NA	+	—
19	1·2	10	6	200	1·1	10	NA	+ +	—
20	1·2	13	8	220	1·0	NA	NA	+ +	+ +
21	1·3	13	11	200	1·1	16	NA	+ +	—
22	1·3	14	11	195	1·1	6	NA	+ +	+ + +
23	1·4	13	10	185	1·2	NA	NA	+ +	—
24	1·5	12	6	200	1·1	NA	NA	—	+ + +
25	1·5	12	10	160	1·3	9	NA	+	—
26	1·5	7	6	195	1·1	NA	NA	+ +	+ +
27	1·5	13	10	185	1·2	18	NA	+	+ +
28	1·7	13	8	155	1·4	NA	NA	+	—
29	1·7	23	10	170	1·3	12	NA	+ + +	+ +
30	1·7	8	6	150	1·4	9	NA	+ +	+ +
31	2·0	7	5	120	1·8	6	NA	+	+ + +
32	2·2	19	10	160	1·4	NA	NA	+ +	—
33	2·3	13	5	130	1·7	NA	NA	—	+ + +
34	2·3	10	4	160	1·4	8	NA	+	—
35	2·3	10	6	160	1·4	NA	NA	+ +	—
36	2·4	8	5	130	1·7	NA	NA	—	+ +
37	2·4	13	10	130	1·7	15	NA	+ +	+ +
38	2·5	6	4	130	1·7	6	NA	—	+ +
39	2·6	11	7	150	1·5	6	NA	+ +	—
40	2·7	12	6	105	2·1	8	NA	+	+ +
41	2·7	18	6	145	1·5	NA	NA	+ + +	—
42	2·8	13	5	115	1·9	NA	NA	+ + +	—
43	2·9	18	7	105	2·1	8	NA	+ + +	—
44	2·9	12	4	105	2·1	13	NA	+ + +	—

AR, aortic regurgitation; MVA, mitral valve area; MR, mitral regurgitation; PHT, pressure half time; NA, not available.

decreasing diastolic pattern is accompanied by a corresponding audio signal, was also assessed by continuous wave Doppler.[6] Artefacts due to excessive noise and wall movements were excluded.[27-29]

CARDIAC CATHETERISATION

Cardiac catheterisation was performed in 32 patients within 24 hours of the Doppler studies. In patients with pure mitral stenosis, mitral valve area was calculated by Gorlin's formula[18] from left ventricular pulmonary capillary wedge pressure recordings and cardiac output was determined by the Fick method. Mitral and aortic regurgitation were assessed by standard angiographic techniques. No attempt was made to calculate mitral valve area in patients with mitral regurgitation. The haemodynamic and Doppler studies were not performed simultaneously.

STATISTICAL ANALYSIS

Cross sectional echocardiographic, continuous Doppler, and cardiac catheterisation data were measured by three different pairs of observers who were unaware of the results of the other studies. We took the mean of each pair of measurements. Mean (SD) interobserver variability was 3 (3)% for the cross sectional echocardiographic mitral valve area and 5 (4)% for Doppler pressure half time; this resembles variability in previous studies.[30 31] Interobserver variability for the haemodynamic mitral valve area was 4 (3)%. When appropriate we analysed the data by analysis of variance, paired and unpaired *t* tests, linear regression, and the non-regression method for assessing agreement between different methods, recently described by Bland and Altman.[32]

Results

PATIENT DATA

Pulsed wave Doppler and angiographic data, when available, showed pure mitral stenosis in 14 patients, mitral stenosis and regurgitation in 15, and mitral stenosis and aortic regurgitation in 15 (10 with and 5 without mitral regurgitation). Mitral regurgitation was graded as 1+ in nine patients, 2+ in 11, and 3+ in five. Pulsed wave Doppler grading of mitral regurgitation was confirmed in 14 of 16 patients undergoing angiography. In two patients the angiographic grade of mitral regurgitation was slightly underestimated by pulsed wave Doppler. Cross sectional echocardiographic mitral valve area was $<1\ \text{cm}^2$ in five patients, from 1 to 1·5 cm in 16, and $>1\cdot5\ \text{cm}^2$ in 23. The table shows the cross sectional echocardiographic, pulsed and continuous wave Doppler, and catheterisation results.

The peak transmitral pressure drop ranged from 7 to 38 mm Hg (mean (SD) 14·7 (8)), the mean transmitral pressure drop ranged from 4 to 21 mm Hg (mean (SD) 7 (3·9)). Peak and mean pressure drops were not significantly different in the 19 patients with mitral stenosis and no mitral regurgitation (including five with aortic regurgitation) (cross sectional echocardiographic mitral valve area 1·6 (0·5) cm^2) and in the 20 patients with associated mi-

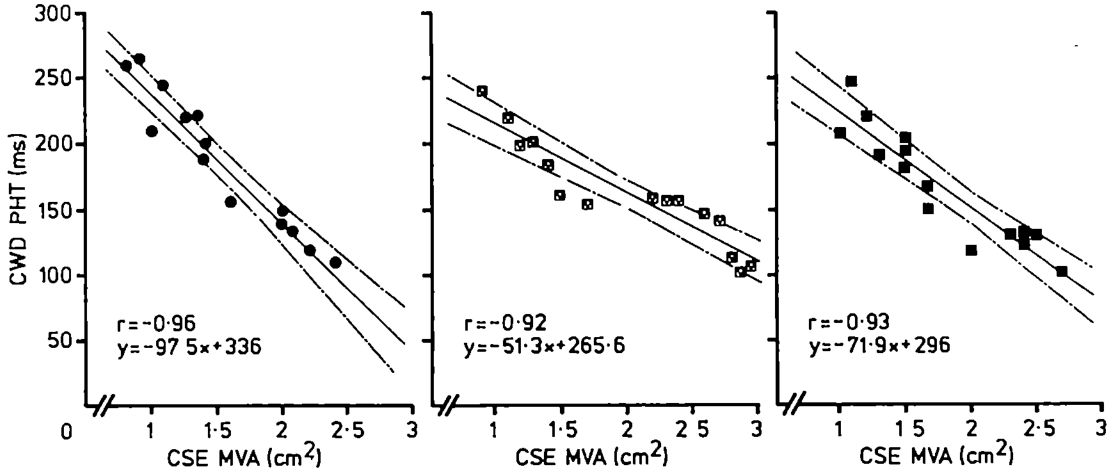

Fig 2 *Regressions between continuous wave Doppler transmitral pressure half time (CWD PHT) and cross sectional echocardiographic mitral valve area (CSE MVA) in patients with pure mitral valve stenosis (●), with associated mitral regurgitation (□), and with aortic regurgitation (■). Broken lines indicate the confidence intervals of the regression line. The slope of regression in patients with pure mitral stenosis was significantly different from that in patients with associated mitral ($p < 0\ 001$) or aortic ($p < 0{\cdot}01$) regurgitation.*

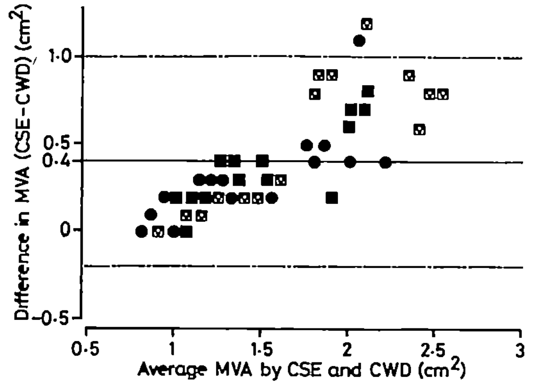

Fig 3 *Agreement between cross sectional echocardiographic (CSE) and continuous wave Doppler (CWD) (220/PHT) estimates of mitral valve area (MVA).*[32] *Difference in mitral valve area (y axis) plotted against the mean value of the two areas (x axis, average mitral valve area) in 44 patients with pure mitral stenosis or mitral stenosis associated with mitral or aortic regurgitation Cross sectional echocardiography overestimated the Doppler area by 0·41 cm^2 (solid line). Broken lines show ±2 SD (−0·2 cm^2 and +1 cm^2). The overestimation by cross sectional echocardiography increases with the size of the mitral valve area Symbols as in fig 2*

tral regurgitation and with a comparable mitral valve area (1·6 (0·5 cm^2) (peak pressure drop 12·2 (5·7) *vs* 14·5 (7·2) mm Hg; mean pressure drop 8·4 (3·9) *vs* 9·3 (3·8) mm Hg)).

TRANSMITRAL PRESSURE DROP AND PRESSURE HALF TIME VERSUS CROSS SECTIONAL ECHOCARDIOGRAPHIC MITRAL VALVE AREA

The cross sectional echocardiographic mitral valve area correlated poorly with peak and mean transmitral pressure drops (r = −0·29 and −0·44 respectively). The correlation between continuous wave Doppler pressure half time and cross sectional echocardiographic mitral valve area was good (r = −0·91; p < 0·001). Figure 2 shows separate regression lines for patients with pure mitral stenosis (r = −0·96), for patients with mitral stenosis and regurgitation (r = −0·92), and for patients with associated aortic regurgitation (r = −0·93). The slope of the regression line for patients with pure mitral stenosis differed significantly from those of the groups with associated mitral (p < 0·001) or aortic valve regurgitation (p < 0·01).

Mean transmitral pressure half time was significantly longer in patients with cross sectional echocardiographic mitral valve area < 1 cm^2 (230 (27) ms) than in those with valve areas of from 1 to 1·5 cm^2 (205 (23) ms) and > 1·5 cm^2 (136 (20) ms) (p < 0·001). When a cross sectional echocardiographic mitral valve area of 1·5 cm^2 was used to distinguish patients with severe stenosis and those with less severe mitral stenosis, a Doppler pressure half time of > 175 ms correctly classified 20 of 21 patients with mitral valve area < 1·5 cm^2. No patient with a cross sectional echocardiographic mitral valve area > 1·5 cm^2 had mitral stenosis classified as severe by continuous wave Doppler.

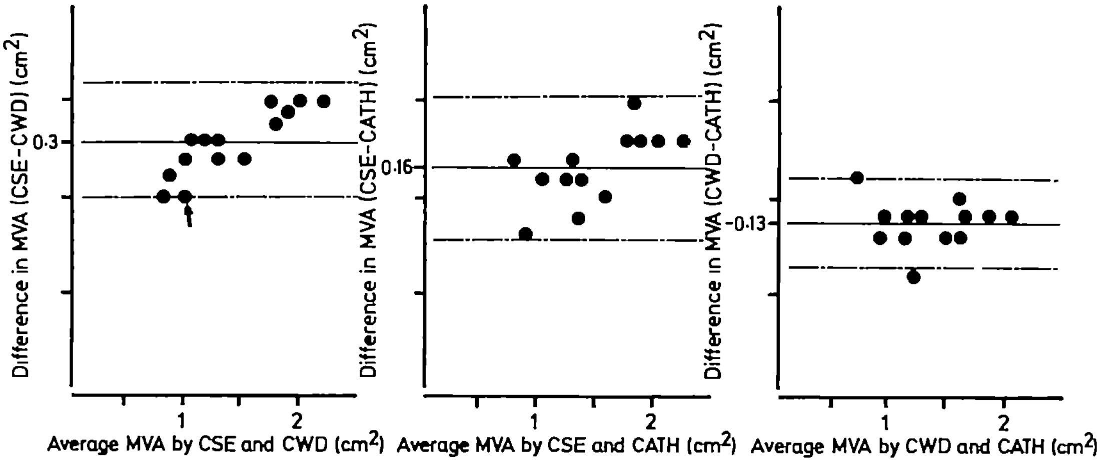

Fig 4 *Plot of the differences between cross sectional echocardiographic (CSE), continuous wave Doppler (CWD), and haemodynamic mitral valve area (Gorlin's formula) in patients with pure mitral valve stenosis (legend and symbols as in fig 3). The arrow indicates a patient with pure mitral stenosis in whom catheterisation was not performed. The haemodynamic area was overestimated by cross sectional echocardiography and underestimated by Doppler. Doppler and haemodynamic estimates, however, agreed more with each other than with echocardiography. Cath = catheterisation.*

CONTINUOUS WAVE DOPPLER VERSUS CROSS SECTIONAL ECHOCARDIOGRAPHIC ESTIMATES OF MITRAL VALVE AREA

We found that a cross sectional echocardiographic mitral valve area of 1 cm^2 corresponded to a transmitral pressure half time (PHT) value of 220 ms. This confirmed results previously reported by Hatle and Angelsen, who found a similar correspondence between cardiac catheterisation and Doppler data.[17] The formula: mitral valve area = 220/PHT (ms), however, underestimated the corresponding echocardiographic mitral valve area by 0·41 (0·30) cm^2 (fig 3). The larger the orifice, the greater the underestimate: 0·2 (0·12) cm^2 (15 (8)% of absolute mitral valve area) in the 25 patients with a cross sectional echocardiographic mitral valve area of <2 cm^2 and 0·70 (0·26) cm^2 (28 (9)%) in the 19 patients with echocardiographic area of >2 cm^2 (12 with associated mitral valve regurgitation) ($p < 0{\cdot}01$) (fig 3). The degree of underestimation was 0·30 (0·15) cm^2 in patients with pure mitral stenosis, 0·56 (0·41) cm^2 in those with combined mitral stenosis and regurgitation, and 0·40 (0·23) cm^2 in the group with associated aortic regurgitation.

ECHOCARDIOGRAPHIC AND DOPPLER ESTIMATES VERSUS CARDIAC CATHETERISATION MITRAL VALVE AREAS IN PATIENTS WITH PURE MITRAL STENOSIS

In fig 4 cross sectional echocardiographic and continuous wave Doppler estimates of mitral valve area in the 13 patients with pure mitral stenosis who underwent cardiac catheterisation are compared with the haemodynamic estimate. Though both cross sectional echocardiographic and Doppler estimates correlated closely with the Gorlin's estimate ($r = 0{\cdot}96$ and 0·94, respectively), cross sectional echocardiography overestimated the haemodynamic area by 0·16 (0·19) cm^2 and Doppler underestimated it by 0·13 (0·12) cm^2 ($p < 0{\cdot}01$).

Discussion

Cross sectional echocardiography gives an accurate assessment of mitral valve area[1,2–4] except in patients with suboptimal images.[3–5] In some patients, however, there is a considerable difference between estimates of mitral valve area by cross sectional echocardiography and by cardiac catheterisation.[4] This has been attributed to limitations of both techniques.[1–8]

Doppler echocardiography can also be used to assess mitral valve area by means of transmitral pressure half time[9,10,13,17]—that is the time required for the diastolic atrioventricular pressure gradient to fall to half its initial value.[33,34] This method has been validated against cardiac catheterisation.[16,17] Catheterisation, however, is not the gold standard for mitral valve area assessment.[1,20–23,33–35] Recently, Smith *et al* reported a good correlation between both Doppler and cross sectional echocardiography and the haemodynamic mitral valve area in patients with unoperated mitral stenosis.[22] In those who had had mitral valvotomy Doppler was more accurate.[22] The influence of associated mitral or aortic regurgitation on the agreement between Doppler and cross sectional echocardiography was not specifically evaluated in the study of Smith *et al.*[22]

We found that Doppler transmitral pressure half time correlated with the cross sectional echocardiographic estimate of mitral valve area. Like other groups,[9,10,13,16,17] we did not find that mitral or aortic regurgitation substantially influenced the degree of this correlation, though they did modify the slope of the regressions. As reported elsewhere,[17] a transmitral pressure half time value of >175 ms was specific in predicting a mitral valve area of $<1{\cdot}5$ cm^2. Further prospective studies are needed to establish the sensitivity and specificity of this criterion.

Hatle *et al* used the empirical formula, 220/PHT, to determine the haemodynamic mitral valve area.[13,17] This formula was reliable for estimating the cross sectional echocardiographic mitral valve area too.[16,17,22] Doppler formula and cross sectional echocardiographic estimates of mitral valve area did not agree completely in our study, however. We found that the Doppler method underestimated the echocardiographic mitral valve area by 15% in patients with valve area of <2 cm^2 and by 28% in those with valve area of >2 cm^2. There are several explanations for differences between our results and those of previous workers.[16,17,22] Firstly, we examined more patients with mild mitral stenosis or with associated severe mitral regurgitation than did previous studies.[13,16,17,22] Even though mitral regurgitation should not per se alter the Doppler estimate of mitral valve area, because transmitral pressure half time is independent of the absolute flow rate,[17] we found that mitral regurgitation influenced the regression between pressure half time and echocardiograhic area. Others have reported that the Doppler formula is less accurate when flow rates are high[36] or mitral regurgitation is present.[37] In our study the degree of Doppler underestimation increased with mitral valve size. Since severe mitral valve regurgitation was seen only in those patients with a mitral valve area >2 cm^2, we could not establish whether valve size or severe mitral regurgitation was the major determinant of Doppler underestimation.

Second, cross sectional echocardiography, Doppler echocardiography, and cardiac catheterisation may not measure the same variable. The exact point at which narrowing of mitral valve complex is maximal may be missed by cross sectional echocardiography, generally in patients with previous commissurotomy.[1,22] Extensive calcification or fibrosis of the submitral apparatus, however, may increase the transmitral gradient to more than the value determined at the level of the leaflet tips.[1,5,17] This condition might result in a large discrepancy between echocardiographic and Doppler or cardiac catheterisation estimates of mitral valve area in patients with severe mitral stenosis, in whom the submitral apparatus is more frequently affected.[1]

The third reason for the disagreement between Doppler and echocardiographic estimates of mitral valve area may be that the empirical Doppler formula, mitral valve area = 220/PHT, does not predict the true anatomical mitral valve area. In previous studies, cross sectional echocardiographic mitral valve area was on average 0·3 cm^2 larger than the cardiac catheterisation estimate.[4,8] It has been suggested that cross sectional echocardiography measures the anatomical mitral valve area, whereas cardiac catheterisation estimates the functional mitral valve area.[1,22] Haemodynamic considerations suggest that the functional area will be somewhat smaller than the anatomical one. In our patients with pure mitral stenosis, Doppler and cardiac catheterisation estimates of mitral area, although not obtained simultaneously, agreed with each other more than with cross sectional echocardiography. Both Doppler and cardiac catheterisation underestimated the echocardiographic area especially in patients with mild mitral stenosis. The different composition of our study group may explain why our results differ from those of Smith *et al* who found that both Doppler and echocardiography overestimated the haemodynamic area in a group of patients who, according to Gorlin's formula, had mitral valve area of $\leqslant 1{\cdot}6$ cm^2 (including a few with severe mitral regurgitation).[22] Our data suggest that the Doppler formula, which is based on a hyperbolic relation between transmitral pressure half time and mitral valve area, is more accurate in predicting the functional mitral valve area, as assessed by cardiac catheterisation, than the anatomical one, as assessed by cross sectional echocardiography. Further studies are needed to evaluate a potential influence of this disagreement between Doppler and cross sectional echocardiography on the clinical decision for or against surgery in patients with moderate mitral valve stenosis.

References

1 Weyman AE. *Cross-sectional echocardiography*. Philadelphia: Lea and Febiger, 1982:146–73.

2 Henry WL, Griffith JM, Michaelis LL, McIntosh CL, Morrow AG, Epstein SE. Measurement of mitral orifice area in patients with mitral valve disease by real-time two-dimensional echocardiography. *Circulation* 1975;**51**:827–31.

3 Nichol PM, Gilbert BW, Kisslo JA. Two-dimensional echocardiographic assessment of mitral stenosis. *Circulation* 1977;**55**:120–33.

4 Wann LS, Weyman AE, Feigenbaum H, Dillon JC, Johnston KW, Eggelton RC. Determination of mitral valve area by cross-sectional echocardiography. *Ann Intern Med* 1978;**88**:337–41.

5 Naito M, Morganroth J, Mardelli TJ, Chen CC, Dreyfus LS. Rheumatic mitral valve stenosis: cross sectional echocardiographic analysis. *Am Heart J* 1980;**100**:34–40.

6 Marino P, Zanolla L, Perini GP, Salazzari GC, Conti F, Poppi A. Critical assessment of two-dimensional echocardiographic estimation of the mitral valve area in rheumatic mitral valve disease: calcific deposits in the valve as a major determinant of the accuracy of the method. *Eur Heart J* 1981;**2**:197–203.

7 Schweizer P, Bardos P, Krebs W, *et al*. Morphometric investigations in mitral stenosis using two dimensional echocardiography. *Br Heart J* 1982;**48**:54–60.

8 Glover MU, Warren SE, Vieweg WVR, Ceretto MJ, Samtoy LM, Hagan AD. M mode and two dimensional echocardiographic correlation with findings at catheterization and surgery in patients with mitral stenosis. *Am Heart J* 1983;**51**:98–102

9 Holen J, Aaslid R, Landmark K, Simonsen S. Determination of pressure gradient in mitral stenosis with a non-invasive ultrasound Doppler technique. *Acta Med Scand* 1976;**199**:445–60.

10 Holen J, Aaslid R, Landmark K, Simonsen S, Ostrem T. Determination of effective orifice area in mitral stenosis from non-invasive ultrasound Doppler data and mitral flow rate. *Acta Med Scand* 1977;**201**:83–8.

11 Kalmanson D, Veyrat C, Bouchareine F, Degroote A. Non-invasive recording of mitral valve flow velocity patterns using pulsed Doppler echocardiography: application to diagnosis and evaluation of mitral valve disease. *Br Heart J* 1977;**39**:517–28.

12 Hatle L, Brubakk A, Tromsdal A, Angelsen B. Noninvasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. *Br Heart J* 1978; **40**:131–40.

13 Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrio-ventricular pressure half-time by Doppler ultrasound. *Circulation* 1979;**60**:1096–104.

14 Diebold B, Theroux P, Bourassa MG, *et al*. Noninvasive pulsed Doppler study of mitral stenosis and mitral regurgitation: preliminary study. *Br Heart J* 1979;**42**:168–75.

15 Thuillez C, Theroux P, Bourassa MG, *et al*. Pulsed Doppler echocardiographic study of mitral stenosis. *Circulation* 1980;**61**:381–7.

16 Stamm RB, Martin RP. Quantification of pressure gradients and areas across stenotic valves by Doppler ultrasound. *J Am Coll Cardiol* 1983;**2**:707–18.

17 Hatle L, Angelsen B. *Doppler ultrasound in cardiology. Physical principles and clinical applications*. Philadelphia: Lea and Febiger, 1985;110–24.

18 Gorlin R, Gorlin SG. Hydraulic formula for calculation

of area of stenotic mitral valve, other cardiac valves and central circulatory shunts. *Am Heart J* 1951;**41**:1–29

19 Selzer A, Willet FM, McCaughey J, Feichtmeir TV. Uses of cardiac catheterization in acquired heart disease. *N Engl J Med* 1957;**257**:121–5.

20 Askenazy J, Carlson J, Alpert JS, Dexter L. Mitral valve area in combined mitral stenosis and regurgitation *Circulation* 1976,**54**:480–3.

21 Denning K, Dacian S, Hall D, Rudolph W. Doppler echocardiographic, 2-dimensional echocardiographic and invasive hemodynamic determination of valve orifice area in mitral valve stenosis. A comparative study [Abstract]. *J Am Coll Cardiol* 1985;**5**:404.

22 Smith M, Handshoe R, Handshoe S, Kwan OL, De Maria AN. Comparative accuracy of two-dimensional echocardiography and Doppler pressure half-time methods in assessing severity of stenosis in patients with and without prior commissurotomy *Circulation* 1986;**73**:100–7.

23 Robson J, Flaxman JC. Measurement of the end-diastolic pressure gradient and mitral valve area in mitral valve stenosis by Doppler ultrasound. *Eur Heart J* 1984;**5**:660–7.

24 Miyatake K, Nimura Y, Sakakibara H, *et al*. Localisation and direction of mitral regurgitant flow in mitral orifice studied with combined use of ultrasonic pulsed Doppler technique and two dimensional echocardiography. *Br Heart J* 1982;**48**:449–58.

25 Veyrat C, Ameur A, Mas S, Lessana A, Abitbol G, Kalmanson D. Pulsed Doppler echocardiographic indices for assessing mitral regurgitation. *Br Heart J* 1984;**51**:130–8.

26 Bommer WJ, Maspes R, Miller L, Mason DT, De Maria AN. Quantification of aortic regurgitation with two-dimensional Doppler echocardiography [Abstract]. *Am J Cardiol* 1981;**47**.412.

27 Esper R Detection of mild aortic regurgitation by range-gated pulsed Doppler echocardiography. *Am J Cardiol* 1982;**50**:1037–43.

28 Veyrat C, Ameur A, Gourtchiglovian C, Lessana A, Abitbol G, Kalmanson D. Calculation of pulsed Doppler left ventricular outflow tract regurgitant index for grading the severity of aortic regurgitation. *Am Heart J* 1984;**108**:507–15.

29 Richards KL, Cannon SR, Crawford MH, Sorensen S. Noninvasive diagnosis of aortic and mitral valve disease with pulsed Doppler spectral analysis. *Am J Cardiol* 1982;**51**:1122–7.

30 Marino P, Zanolla L, Nidasio GP, Nicolosi GL, Fabbri A. Interpretative reproducibility of two dimensional echocardiographic images. Analysis of intraobserver and beat to beat reproducibility of the mitral valve orifice. *Eur Heart J* 1983;**4**:733–7.

31 Gardin JM, Dabestani A, Matin K, Allfie A, Russell D, Henry WL. Reproducibility of Doppler aortic blood flow measurements: studies on intraobserver, interobserver and day-to-day variability in normal subjects. *Am J Cardiol* 1984;**54**:1092–8.

32 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**i**:307–10.

33 Libanoff AJ, Rodbard S. Evaluation of the severity of mitral stenosis and regurgitation. *Circulation* 1966;**33**:218–26.

34 Libanoff AJ, Rodbard S. Atrioventricular pressure half-time. Measure of mitral valve orifice area. *Circulation* 1968;**38**:144–50.

35 Seitz WS, Hosenpud J, Schutz R. An orifice formula independent of mitral pressure gradient for the evaluation of prosthetic mitral valve obstruction. *Eur Heart J* 1984;**5**.932–40.

36 Sagar KB, Wann LS. Doppler mitral pressure half-time is not an independent predictor of mitral valve area [Abstract]. *J Am Coll Cardiol* 1986;**7**:61A.

37 Gonzales MA, Child JS, Krivokapich J. Quantification of mitral stenosis: a comparative study of two-dimensional and Doppler echocardiography and intracardiac hemodynamics [Abstract] *J Am Coll Cardiol* 1986;**7**:61A.

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Ten year clinical evaluation of Starr-Edwards 2400 and 1260 aortic valve prostheses

DAVID HACKETT, IOANNIS FESSATIDIS, RALPH SAPSFORD, CELIA OAKLEY

From the Departments of Clinical Cardiology and Cardiac Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY The long term performance characteristics of the 2400 and 1260 series of Starr-Edwards aortic prostheses were investigated by a follow up study of clinical outcome of 327 patients discharged from hospital with isolated aortic valve replacement. Follow up lasted for up to 10 years and was based on 1616 patient-years. The 2400 series cloth covered tracked valve was implanted in 182 patients from 1974 to 1980 and the 1260 series bare strut silastic ball valve was inserted in 145 patients from 1979 to 1983. Total 10 year mortality and valve related morbidity were low and no cases of mechanical valve failure were recorded. There were no significant actuarial differences in mortality or valve related morbidity between the 2400 and 1260 valves.

Starr-Edwards models 2400 and 1260 aortic valve prostheses showed excellent durability without any mechanical failures over a 10 year period. The long term outcome of isolated aortic valve replacement with these models is associated with a low frequency of valve related complications.

Many different mechanical and tissue prostheses are now available for aortic valve replacement and although efforts continue to be made to design durable heart valve prostheses that are free from valve related complications the debate continues about the reported advantages of low profile prostheses or biological valves compared with caged ball valves.[1] The long term structural durability and consistent long term integrity of xenografts have yet to be demonstrated.[2] Mechanical heart valve prostheses have reasonable records of structural durability but this advantage is compromised by the risk of thromboembolism and the need for indefinite anticoagulation with its inherent risks.[3 4] In patients with chronic mitral valve disease, indefinite anticoagulation is frequently necessary whether or not mitral valve operation is undertaken, and mechanical prostheses are usually chosen for mitral valve replacement because they are more durable than xenografts. Patients with isolated aortic valve disease, however, only require indefinite anticoagulation when mechanical prostheses are implanted; in these patients the choice between mechanical and tissue aortic valve prostheses is not so clear cut.

Starr-Edwards aortic valve prostheses have been implanted clinically since 1960 and the model 1200 series dating from 1966 has demonstrated a lower frequency of mechanical dysfunction and thromboembolism than earlier models. Many large series of patients followed up after isolated Starr-Edwards aortic valve replacement have now confirmed these findings.[5−7] Since 1973 we have had extensive experience with the modern series of Starr-Edwards aortic prostheses. The 2400 model cloth covered tracked valve with stellite poppet, which was designed to reduce cloth wear, was introduced in 1972 and was frequently implanted in patients at this hospital until 1980 when it was withdrawn from general use by the manufacturers because it had no apparent advantages over the 1260 prosthesis. The 1260 model bare strut silastic ball valve with reduced metal on the inflow surface was introduced in 1968, and continues to be used for aortic valve replacement.

This study was undertaken to examine the long term performance characteristics of models 2400 and 1260 Starr-Edwards aortic valve prostheses and to provide specific data which may be used to compare the clinical performance of other mechanical and tissue prostheses. The aim of this study was to

Requests for reprints to Dr David Hackett, Department of Cardiology, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS.

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consider long term clinical follow up and to relate this to the specific prosthesis used.

Patients and methods

We reviewed the records of all 993 patients who had cardiac valve prostheses inserted at Hammersmith Hospital between January 1974 and December 1983 and identified 689 cases where a Starr-Edwards valve was inserted. Of these there were 352 consecutive patients discharged alive from hospital who had an isolated aortic valve replacement by a Starr-Edwards model 2400 or 1260 prosthesis. During this period only four patients (in 1974) had a Starr-Edwards aortic valve replacement with a model other than 2400 or 1260; all four had Starr-Edwards model 2320 non-tracked cloth covered strut metallic ball prostheses and have been excluded from analysis.

The decision to insert a Starr-Edwards prosthesis in the aortic position in these patients was based on several factors. The need for indefinite anticoagulation, an adequate size of aortic root, and the attending cardiologists and cardiac surgeons preference for these prostheses were the most important considerations during this period. Those patients with an aortic root of inadequate size to encompass a caged ball (Starr-Edwards) valve usually had a disc valve (Björk-Shiley) implanted. In general, mechanical prostheses were favoured particularly in younger patients because of their more certain durability whereas xenograft bioprostheses were usually only implanted in those aged over 70 years or in those few patients with specific contraindications to indefinite anticoagulation.

Patients with multiple valve replacements were excluded from this study but the total includes patients undergoing combined procedures, such as open mitral valvotomy or aortocoronary bypass grafting. Operative techniques were standardised and from 1974–78 included myocardial protection by systemic hypothermia, aortic cross clamping, and a beating perfused heart at 28°C. After 1978 systemic hypothermia at 28°C and myocardial preservation at 4–10°C with the use of St Thomas's cardioplegic solution was used. Interrupted sutures were almost always used to insert the prosthetic valve. All patients were routinely anticoagulated with warfarin immediately after operation and this was continued indefinitely. Anticoagulation was aimed to maintain standardised British corrected prothrombin ratios in the therapeutic range of 2·5–4·0 times control values.

As the aim of this study was to determine long term outcome in relation to the prosthesis implanted, immediate perioperative and early postoperative non-valve related morbidity and mortality were not analysed and follow up was started from the time of hospital discharge. Patient follow up was obtained retrospectively and by physicians in all cases. Sources of this included records from Hammersmith Hospital cardiac follow up clinics, referral hospital clinics, and in some cases family practitioners. At operation sex, age, rhythm, functional class,[8] pathology and aetiology of aortic valve disease, previous heart valve prostheses, and associated operative procedures were recorded. Follow up evaluation was continued up to December 1983. The following were analysed: *(a)* death and its cause if known from clinical and/or necropsy evidence; *(b)* reoperation to replace the Starr-Edwards prosthesis, and its indication; *(c)* the presence of the following complications at *any time* postoperatively—thromboembolism including *any* sudden focal transient or permanent neurological deficit, anticoagulant related haemorrhage requiring active medical management including blood transfusion or hospital admission, prosthetic valve endocarditis as defined by standard criteris,[9] primary valve failure resulting in mechanical dysfunction (such as valve occlusion or ball variance) including thrombosis in situ, valve related intravascular haemolysis requiring active medical management including hospital admission or detailed outpatient management, and haemodynamically severe paraprosthetic regurgitation requiring admission or detailed outpatient management.

The significance of univariate analysis was tested with the χ^2 test. Standard non-parametric actuarial (Kaplan-Meier) and linearised statistical techniques were used to describe survival and the incidence of valve-related complications.[10 11] Actuarial probability estimates were analysed by the Biomedical Data Package Program (BMDP1L) of the University of California and are presented as mean rates plus or minus one SEM. The Wilcoxon rank test was used for statistical comparisons of actuarial curves.

Results

We followed up 327 patients (92·8% complete) up to December 1983—a cumulative total of 1616 patient-years. Most of the patients lost to follow up were living overseas and have not been selected out on any specific criteria. One hundred and eighty two (55·7%) patients had Starr-Edwards model 2400 inserted during 1974–80 and 145 (44·3%) had a Starr-Edwards model 1260 inserted during 1979–83 (fig 1). Table 1 lists the clinical, operative, and pathophysiological characteristics of the patients. The aortic valve disease was considered to be congenital in 33·9% of the total with a rheumatic

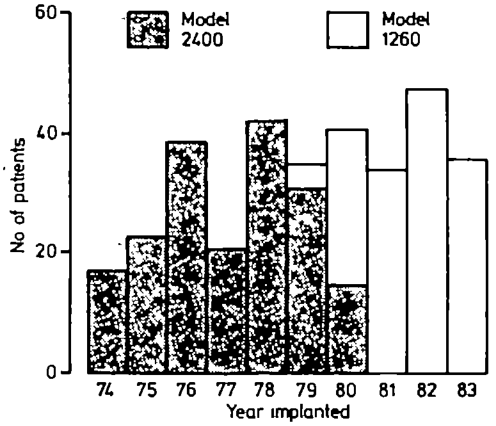

Fig 1 *Numbers of patients with isolated Starr-Edwards aortic valve replacement by year and model.*

aetiology in only 22·9%. The proportion of patients with congenital aortic valve disease, however, was significantly greater in those undergoing valve replacement with model 2400 prosthesis (40·7% *vs* 25·5%, $p < 0·05$). At the time of aortic valve replacement associated procedures were performed in 26·6% of the patients, most commonly aortocoronary bypass grafting in 14·4% of the total. Aortocoronary bypass grafting was performed in significantly more of those patients undergoing valve replacement with model 1260 prothesis (24·1% *vs* 6·6%, $p < 0·001$). There were no other significant differences in clinical, pathophysiological, or operative characteristics between those patients with a model 2400 prosthesis and with model 1260.

During 10 years of follow up 47 patients died (2·9%/patient-year) (table 2). In 38 cases the cause of death could be established from clinical and/or necropsy evidence. In 27 patients this was due to cardiac causes. Most cardiac deaths were associated with the effects of chronic heart failure but in four cases death could be related to the Starr-Edwards aortic prosthesis, all four being due to thromboembolism. Four deaths were indirectly valve related—three resulting from infective endocarditis which had not be eradicated either medically or by reoperation to replace the Starr-Edwards aortic prosthesis. One anticoagulant related death was due

Table 1 *Clinical, pathophysiological, and operative characteristics in patients with Starr-Edwards 2400 and 1260 aortic valve prostheses*

	2400		*1260*		*Total*	
Data	*No*	%	*No*	%	*No*	%
Patients	182	55·7	145	44·3	327	100·0
Patient-years followed up.						
5 years	368	51·1	352	48·9	720	44·6
10 years	1264	78·2	—	—	1616	100·0
Mean age (range)	53·6 (14–77)		50·8 (19–78)		52·1 (14–78)	
Male	128	70·3	109	75·2	237	72·5
Rhythm						
SR	165	90·7	127	87·6	292	89·3
AF	17	9·3	18	12·4	35	10·7
Functional class						
I	20	11·0	12	8·3	32	9·8
II	97	53·3	74	51·0	171	52·3
III	55	30·2	46	31·7	101	30·9
IV	10	5·5	13	9·0	23	7·0
Pathology:						
AS	95	52·2	75	51·7	170	52·0
AR	52	28·6	46	31·7	98	30·0
AS + AR	35	19·2	24	16·6	59	18·0
Aetiology:						
Rheumatic	40	22·0	35	24·1	75	22·9
Congenital	74	40·7*	37	25·5*	111	33·9
Degenerative	49	26·9	52	35·9	101	30·9
IE	15	8·2	20	13·8	35	10·7
Others	4	2·2	1	0·7	5	1·5
Previous prosthesis:						
AVR	8	4·4	13	9·0	21	6·4
MVR	1	0·5	0	0	1	0·3
Associated procedures:						
CABG	12	6·6*	35	24·1*	47	14·4
OMV	8	4·4	11	7·5	19	5·8
Aorta resect	6	3·3	2	1·4	8	2·4
Others	5	2·7	8	5·5	13	4·0

SR, sinus rhythm, AF, atrial fibrillation/flutter; AS, aortic stenosis; AR, aortic regurgitation, AS + AR, aortic stenosis and regurgitation; IE, infective endocarditis, AVR, aortic valve replacement; MVR, mitral valve replacement; CABG, coronary artery bypass grafting; OMV, open mitral valvotomy; aorta resect, aortic root replacement.
$^*p < 0·05$ for 2400 *vs* 1260.

Table 2 *Mortality in patients with Starr-Edwards 2400 and 1260 aortic valve prostheses*

Data	*2400*		*1260*		*Total*	
	No	*%/pt-yr*	*No*	*%/pt-yr*	*No*	*%/pt-yr*
Total mortality:						
At 5 years	26	7·07	15	4·26	41	5·69
At 10 years	32	2·53	—	—	47	2·91
Causes:						
Cardiac	18	1·42	9	2·56	27	1·67
Sudden	1	0·08	1	0·28	2	0·12
Valve related	3	0·24	1	0·28	4	0·25
Not valve related	14	1·11	7	1·99	21	1·30
Not cardiac	5	0·40	2	0·57	7	0·43
Not known	9	0·71	4	1·14	13	0·80
Total	32	2·53	15	4·26	47	2·91
Actuarial survival (mean (SEM)) (%)						
At 5 years	83 (3)*		89 (4)*		84 (2)	
At 10 years	72 (5)				73 (5)	

pt-yr, patient-years. *p = 0·15 for 2400 *vs* 1260

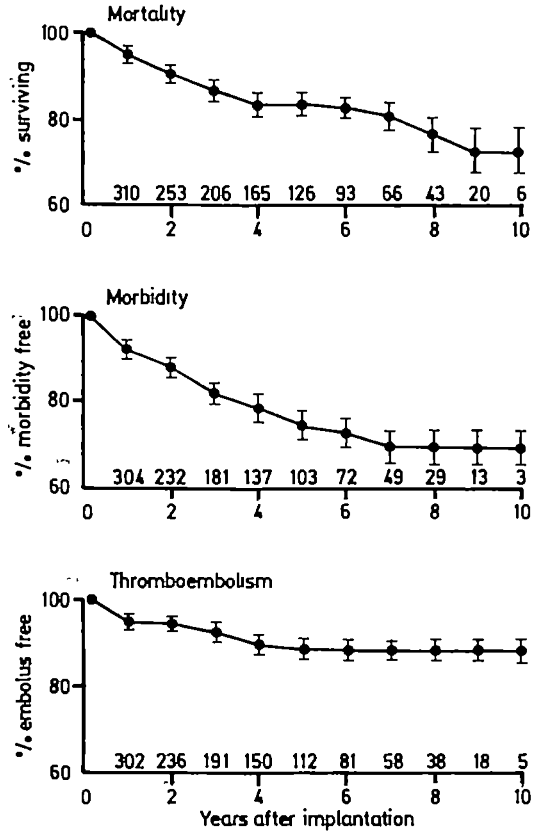

Fig 2 *Actuarial estimates of survival, freedom from valve related morbidity, and freedom from thromboembolism for all patients up to 10 years after aortic valve replacement (means (1 SEM)). The total numbers of patients at risk each year are shown above the abscissa. Most valve related complications occurred early after implanatation of the Starr-Edwards aortic valve and no new thromboembolic events were seen after 5 years.*

to a mid-brain pontine haemorrhage. No deaths could be attributed to paraprosthetic regurgitation or haemolysis and no deaths from primary valve failure caused by mechanical dysfunction or thrombosis in situ were documented. Actuarial estimates of survival were 84 (2)% at five years and 73 (5)% at 10 years (fig 2).

Table 3 lists the valve related complications that were observed. No cases of primary valve failure caused by mechanical dysfunction or thrombosis in situ were reported. Over 10 years valve related morbidity was documented in 60 patients (3·71%/patient-year). Thromboembolism, noted in 22 patients (1·36%/patient-year), was the most frequent complication. The central nervous system was affected in 18 (82%) cases and in four cases myocardial infarction was assumed to result from thromboembolism to the coronary circulation. Coronary arteriography in three of the latter cases was normal either before or after the event. Ten of the 18 cases of non-fatal thromboembolism to the central nervous system resulted in a severe permanent residual neurological deficit. Transient ischaemic attacks of the central nervous system were recorded in eight patients, all without permanent neurological deficit including four patients who complained of amaurosis fugax. Thromboembolism was not significantly correlated with the presence of atrial fibrillation; the combination occurred in only two patients. Thromboembolic events were observed in a total of 26 patients over 10 years (1·61%/patient-year) including the four who died of thromboembolism to the central nervous system (table 4). In all 26 patients these events were observed within five years of the Starr-Edwards aortic valve implantation. Actuarial estimates of freedom from thromboembolic events were 89 (2)% at five and also at 10 years (fig 2).

Anticoagulant related haemorrhage was reported in 12 patients (0·74%/patient-year), prosthetic valve

Table 3 *Valve related morbidity in patients with Starr-Edwards 2400 and 1260 aortic valve prostheses*

	2400		*1260*		*Total*	
Data	*No*	*%/pt-yr*	*No*	*%/pt-yr*	*No*	*%/pt-yr*
Total valve related morbidity:						
At 5 years	33	8·97	22	6·25	55	7·64
At 10 years	38	3·01	—	—	60	3·71
Causes:						
Thromboembolism	12	0·95	10	2·84	22	1·36
CNS	11	0·87	7	1·99	18	1·11
Non-CNS	1	0·08	3	0·85	4	0·25
Anticoag haem	9	0·71	3	0·85	12	0·74
Prosth endoc	10	0·79	4	1·14	14	0·87
Haemolysis	3	0·24	0	0	3	0·19
Paraprosth reg	4	0·32	5	1·42	9	0·56
Mechan failure	0	0	0	0	0	0
Total	38	3·01	22	6·25	60	3·71
Reoperation:						
Thromboembolism	5	0·40	4	1·14	9	0·56
Prosth endoc	4	0·32	4	1·14	8	0·49
Paraprosth reg	2	0·16	5	1·42	7	0·43
Total	11	0·87	13	3·69	24	1·49
Actuarial freedom from morbidity (mean (SEM) to (%):						
At 5 years	74(3)*		84(4)*		75(3)	
At 10 years	69(4)				70(4)	

CNS, central nervous system, non-CNS, non-central nervous system; anticoag haem, anticoagulant related haemorrhage; prosth endoc, prosthetic endocarditis; paraprosth reg, paraprosthetic regurgitation; mechan failure, mechanical failure; pt-yr, patient-years.
*p = 0·21 for 2400 *vs* 1260.

endocarditis in 14 (0·87%/patient-year), haemolysis in three (0·19%/patient-year), and paraprosthetic regurgitation without endocarditis in nine (0·56%/patient-year). Actuarial estimates of freedom from all valve related morbidity were 75 (3)% at five years and 70 (4)% at 10 years (fig 2).

Twenty four patients required reoperation (1·49%/patient-year) (table 3). The causes were thromboembolism in nine patients, prosthetic valve endocarditis in eight (with some but haemodynamically not severe paraprosthetic regurgitation in three of these), and severe paraprosthetic regurgitation without infection in seven. In all but one patient (with paraprosthetic regurgitation), reoperation was performed within 12 months of the original aortic valve replacement. Three patients reoperated on for continuing infective endocarditis died at operation or shortly afterwards, and there was one late death (at one year) after reoperation for paraprosthetic regurgitation in a patient with Marfan's syndrome.

The incidence of mortality and valve related morbidity did not appear to be particularly high in any specific year. There were no significant differences evident between the 2400 and 1260 prostheses in the actuarial probability of mortality, valve related morbidity, or thromboembolic events. A consistent trend towards greater freedom from mortality and valve related complications, however, is apparent for the model 1260 prosthesis over the period 1979–83 compared with the 2400 prosthesis during 1974–78 (fig 3).

Table 4 *Total thromboembolic events in patients with Starr-Edwards 2400 and 1260 aortic valve prostheses*

	2400		*1260*		*Total*	
	No	*%/pt-yr*	*No*	*%/pt-yr*	*No*	*%/pt-yr*
	Total thromboembolic events					
At 5 years	12	3·26	11	3·13	23	3·19
At 10 years	15	1·19	—	—	26	1·61
	Actuarial freedom from thromboembolism (mean (SEM)) (%)					
At 5 years	89(3)*		93(3)*		89(2)	
At 10 years	89(3)				89(2)	

pt-yr, patient-years. *p = 0·61 for 2400 *vs* 1260.

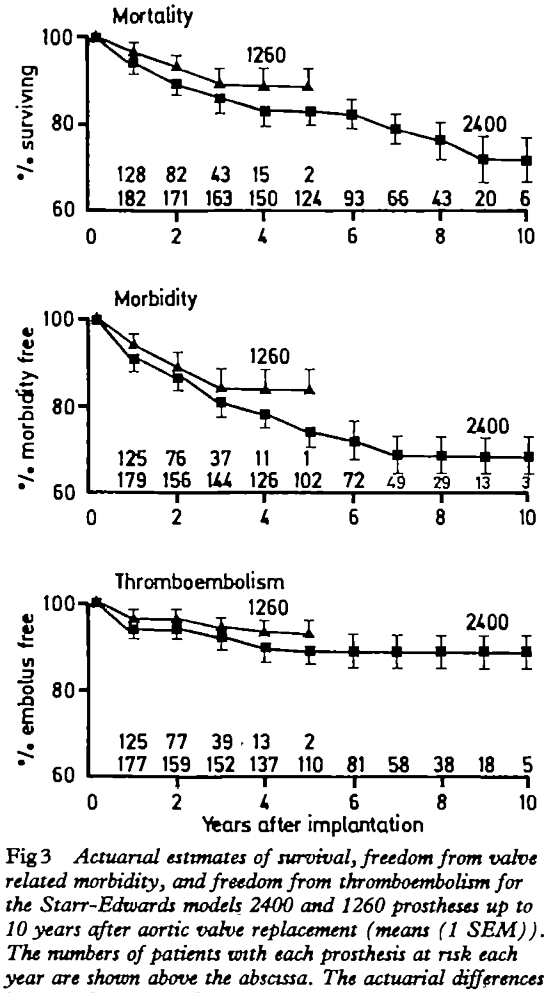

Fig 3 *Actuarial estimates of survival, freedom from valve related morbidity, and freedom from thromboembolism for the Starr-Edwards models 2400 and 1260 prostheses up to 10 years after aortic valve replacement (means (1 SEM)). The numbers of patients with each prosthesis at risk each year are shown above the abscissa. The actuarial differences between the 1260 and 2400 prostheses are not statistically significant, but there is a consistent trend towards greater freedom from mortality and valve related complications for the 1260 prosthesis (during 1979–83) compared with the 2400 model (during 1974–78).*

Discussion

This study was performed to define the long term performance characteristics of the modern series of Starr-Edwards aortic valve prostheses and demonstrates that the structural durability of Starr-Edwards models 2400 and 1260 aortic prostheses is excellent. There were no reports of cases of mechanical dysfunction from failures such as poppet fracture or embolisation, strut fracture, ball variance, or thrombosis in situ. This accords with other studies of the long term follow up of the modern series of Starr-Edwards aortic prostheses, with no previous reports of strut fractures and negligible frequency of variance of the silastic balls.[5–7] Thrombosis in situ seems to be very rare in anticoagulated patients with these prostheses.[7 12] The late mortality of our patients with Starr-Edwards aortic valve replacement is similar to that reported in other large series and the actuarial survival estimates compare favourably.[5–7] Although most deaths were from cardiac causes, the Starr-Edwards prosthesis could only be implicated in four (0·25%/patient-year) of these due to thromboembolism. When the cause of death was known, this could be indirectly related to the Starr-Edwards valve replacement in only six patients (three cases of infective endocarditis, two sudden deaths, and one intracranial haemorrhage). Even if such indirectly related deaths are included, valve related mortality over 10 years still remains low (0·62%/patient-year).

Thromboembolism is the most important complication to follow from insertion of mechanical cardiac valve prostheses.[3 4 13] In this series we recorded a thromboembolic event (according to a comprehensive definition) in 26 patients of which only four were fatal. The frequency of thromboembolism is low compared with other published series.[5–7] Anticoagulation in these patients was deliberately maintained in the upper part of the therapeutic range (2·5–4·0 times control values) in order to reduce as far as possible the risk of thromboembolism which, if it should occur, may be fatal or result in permanent morbidity. The low frequency of thromboembolism in our series may be attributed in part to the careful anticoagulant control achieved by anticoagulant clinics and to the discipline of the patients. This may be an important factor in determining the choice of valve prosthesis in different countries.

The frequency of anticoagulant related haemorrhage in our series was low. There was one fatal case of pontine haemorrhage but there were no other recorded episodes of intracranial bleeding. Most haemorrhages were gastrointestinal (nine patients), but this was rarely spontaneous and usually a precipitating event could be identified and no serious bleeding complications were observed. Other sites of haemorrhage were intramesenteric and retroperitoneal (one patient each). Anticoagulant problems associated with pregnancy, childbirth, or fetal abnormalities were not included in our analysis but the number of women of childbearing age with Starr-Edwards prostheses in our series was small and anticoagulant problems associated with unrelated (non-cardiac) operations were rare. The low frequency of anticoagulant related haemorrhage in this study favourably compares with that of other published series[5–7] and again may relate, in part, to careful anticoagulant control.

Prosthetic valve endocarditis developed in 14 patients; in three cases this was fatal. A wide variety of organisms was responsible, and the variation in the interval between valve replacement and the development of infective endocarditis reflects the usual experience in series of prosthetic valve endocarditis. Six patients required reoperation for endocarditis on eleven occasions, illustrating the surgical difficulty of eradicating the organism when medical treated has failed.[9 14] One patient required reoperation on four occasions for endocarditis, but now is well three years after the last operation.

Haemolysis requiring hospital admission or detailed outpatient management was recorded in only three patients. In only one patient was this associated with appreciable paraprosthetic regurgitation. Haemolysis per se was never an indication for reoperation in this series. Appreciable paraprosthetic regurgitation was noted in nine patients of whom seven required reoperation. In two cases paraprosthetic regurgitation appeared after reoperation for prosthetic valve endocarditis, a situation in which the risk of prosthetic dehiscence is high. Reoperation for all but one of the patients (with prosthetic regurgitation) was necessary within the first year after Starr-Edwards aortic valve replacement, confirming that in the absence of endocarditis, paraprosthetic regurgitation probably results from technical factors relating to operation and is not prosthesis related. The frequency for reoperation was low at 1·49%/patient-year, the indications being almost equally divided among thromboembolism, prosthetic endocarditis, and paraprosthetic regurgitation. Mortality and morbidity after reoperation again probably reflect the underlying aetiology and the patient's condition rather than prosthesis specific events.

In this study there was a consistent, although statistically insignificant, trend towards implantation of the model 1260 being associated with less mortality and fewer valve related complications including thromboembolic events than the 2400 aortic prosthesis. The 1260 prostheses were all implanted during the period 1979–83, however, whereas the 2400 valves were inserted during 1974–80. Thus our data do not establish whether the trend observed in this study was caused by differences in patient related factors including general improvements in surgery and patient care over these periods of time, or was a genuine but statistically insignificant difference between valve models, or was due to chance. Many patient related factors have been shown significantly to predict a greater probability of developing long term complications.[15 16] Several studies have reported a lower incidence of mortality and thromboembolism for the same prosthesis in patients who had aortic valve replacement performed recently than in comparable patients operated on in earlier years.[5 17] The risk of systemic thromboembolism is high in patients with severe myocardial impairment,[18] and indeed spontaneous calcific embolisation can occur in the unoperated patient with calcific aortic stenosis.[19] Older age and chronic severe aortic regurgitation are associated with a considerable reduction in expected longevity.[16] The risk of developing prosthetic endocarditis is generally independent of the type of prosthesis implanted and the choice of valve for patients with infective endocarditis remains difficult because opinions differ about the risk of recurrence associated with various protheses.[14 20 21]

Differences in mortality and valve related morbidity in our patients compared with other published series are unlikely to be explained by differences in patient populations, because our patients resembled those in other series in terms of sex, rhythm, functional class, aetiology, and pathology; however, our patients tended to be younger.[5–7] In one study the Starr-Edwards prostheses were implanted as a valve of second choice in patients with more complicated diagnoses and a high proportion of previous valve surgery which may account for their relatively poor outcome in that study.[5] Apart from functional class, the severity of preoperative or postoperative valvar disease or myocardial function was not considered in this study, but we have no reason to suspect significant differences from other series which would explain differences in mortality or valve related complications.

Prosthesis related factors that determine mortality and morbidity include reliability, durability, and thromboembolism. No cases of mechanical prosthetic dysfunction were reported in this study, and the frequency of thromboembolism was low. Compared with mechanical protheses bioprostheses used for aortic valve replacement show a lower incidence of thromboembolism and are not associated with any anticoagulant related haemorrhages; but these advantages are compromised by the increasing need for reoperation because of primary tissue valve failure with time. The rate of primary tissue valve failure accelerates after six years when the incidence of reoperation exceeds that for mechanical aortic prostheses,[22] and the incidence of primary tissue valve failure for bioprostheses is 20–30% at 10 years.[23] There was no statistically significant difference between aortic bioprostheses and the Starr-Edwards 1260 prosthesis in total rates of valve failure at eight years.[22] Thus for isolated aortic valve replacement there seemed little to choose between mechanical and tissue prostheses up to eight years afterwards, but the Starr-Edwards 1260 valve was more reliable and durable in the longer term.[7]

In summary, the long term structural reliability and durability of the Starr-Edwards models 1260 and 2400 aortic prostheses is excellent. No episodes of mechanical valve failure or thrombosis in situ were observed and actuarial survival estimates of patients with these prostheses compare very favourably with those of other workers.[5-7] The frequency of thromboembolic events in this study was less than that reported elsewhere, and the frequency of haemorrhagic complications associated with indefinite anticoagulation was also low. Like others, however, we realise that structural durability is only one of many variables to consider when assessing the performance of prostheses.[7] This series will provide a basis for the comparison of newer valve substitutes, particularly bioprostheses, whose long term structural durability has yet to be established.[1 2 13]

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References

1 Tepley JF, Grunkemeier GL, Sutherland HD'A, Lambert LE, Johnson VA, Starr A. The ultimate prognosis after valve replacement: an assessment at twenty years. *Ann Thorac Surg* 1981;**32**:111–7.

2 Oyer PE, Stinson EB, Griepp RB, Shumway NE. Valve replacement with the Starr-Edwards and Hancock prostheses: comparative analysis of late morbidity and mortality. *Ann Surg* 1977;**186**:301–9.

3 Edmunds LH. Thromboembolic complications of current cardiac valvular prostheses. *Ann Thorac Surg* 1982;**34**:96–106.

4 Fuster V, Pumphrey CW, McGoon MD, Chesebro JH, Pluth JR, McGoon DC. Systemic thromboembolism in mitral and aortic Starr-Edwards prostheses. A 10–19 year follow-up. *Circulation* 1982;**66**(suppl I):157–61.

5 Wain WH, Drury PJ, Ross DN. Aortic valve replacement with Starr-Edwards valves over 14 years. *Ann Thorac Surg* 1982;**33**:562–9.

6 Starr A, Grunkemeier GL, Lambert LE, Thomas DR, Suginura S, Lefrak EA. Aortic valve replacement: a ten-year follow-up of non-cloth-covered vs cloth-covered caged-ball prostheses. *Cardiovasc Surg* 1977;**56**(suppl 2):133–9.

7 Miller DC, Oyer PE, Mitchell RS, *et al.* Performance characteristics of the Starr-Edwards Model 1260 aortic valve prosthesis beyond ten years. *J Thorac Cardiovasc Surg* 1984;**88**:193–207.

8 The criteria committee of the New York Heart Association. *Diseases of the heart and blood vessels; nomenclature and criteria for diagnosis.* 6th ed. Boston: Little, Brown, 1964.

9 Baumgartner WA, Miller DC, Reitz BA, *et al.* Surgical treatment of prosthetic valve endocarditis. *Ann Thorac Surg* 1983;**35**:87–102.

10 Kaplan EL, Meier P. Non parametric estimations from incomplete observations. *J Am Stat Assoc* 1958;**53**. 457–81.

11 Gehan EA. Generalised Wilcoxon test for comparing arbitrary singly-censored samples. *Biometrica* 1965; **52**:203–23.

12 Metzdorff MT, Grunkemeier GL, Pinson CW, Starr A. Thrombosis of mechanical cardiac valves: a qualitative comparison of the silastic ball valve and the tilting disc valve. *J Am Coll Cardiol* 1984;**4**:50–3.

13 Bodner E, Wain WH, Haberman S. Assessment and comparison of the performance of cardiac valves. *Ann Thorac Surg* 1982;**34**:146–56.

14 Ivert TSA, Dismukes WE, Cobbs CG, Blackstone EH, Kirklin JW, Bergdahl LAL. Prosthetic valve endocarditis. *Circulation* 1984;**69**:223–32.

15 MacManus Q, Grunkemeier GL, Lambert LE, Teply JF, Harlan BJ, Starr A. Year of operation as a risk factor in the late results of valve replacement. *J Thorac Cardiovasc Surg* 1980;**80**:834–41.

16 Mitchell RS, Miller DC, Stinson EB, *et al.* Significant patient-related determinants of prosthetic valve performance. *J Thorac Cardiovasc Surg* 1986;**91**:807–17.

17 Starr A. The Starr-Edwards valve. *J Am Coll Cardiol* 1985;**6**:899–903.

18 Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981;**47**:525–31.

19 Holley KE, Bahn RC, McGoon DC, Mankin HT. Spontaneous calcific embolisation associated with calcific aortic stenosis. *Circulation* 1963;**27**:197–200.

20 Rutledge R, Kim BJ, Applebaum RE. Actuarial analysis of the risk of prosthetic valve endocarditis in 1598 patients with mechanical and bioprosthetic valves. *Arch Surg* 1985;**120**:469–72.

21 Sweeney MS, Reul GJ, Cooley DA, *et al.* Comparison of bioprosthetic and mechanical valve replacement for active endocarditis. *J Thorac Cardiovasc Surg* 1985;**90**:676–80.

22 Perier P, Bessou JP, Swanson JS, *et al.* Comparative evaluation of aortic valve replacement with Starr, Björk, and porcine valve prostheses. *Circulation* 1985;**72**(suppl II):140–5.

23 McGilligan DJ, Lewis JW, Heinzerling RH, Smith D. Fate of a second porcine bioprosthesis valve. *J Thorac Cardiovasc Surg* 1983;**85**:362–70.

Br Heart J 1987;57:364–70

The dysplastic pulmonary valve: echocardiographic features and results of balloon dilatation

NORMAN N MUSEWE, MURRAY A ROBERTSON, LEE N BENSON,
JEFFREY F SMALLHORN, PATRICIA E BURROWS,* ROBERT M FREEDOM,
C A F MOES,* RICHARD D ROWE

From the Division of Cardiology, Variety Club Cardiac Catheterization Laboratories, Hospital for Sick Children, Toronto; and the Department of Paediatrics, University of Toronto Faculty of Medicine, Ontario, Canada

SUMMARY The feasibility of using balloon dilatation to relieve stenosis caused by dysplasia of the pulmonary valve was assessed in seven patients (five female, mean age two years) with angiographically confirmed dysplasia who were identified among 38 patients with pulmonary valve stenosis selected for balloon dilatation over a two year period. The clinical features in three patients were consistent with Noonan's syndrome. In all patients the gradient across the valve was assessed by cross sectional echocardiography and Doppler echocardiography before cardiac catheterisation. Balloon dilatation was performed by conventional techniques. In one patient, who had balloon dilatation in the operating room before surgical valvectomy, the diameter of the valve orifice increased from 3 mm to 10 mm. Inspection showed a tear along the anterior commissure. The mean (SD) pressure gradients between the right ventricle and pulmonary artery before and immediately after dilatation in five patients were not significantly different (58 (28) and 47 (12) mm Hg) respectively. There was no overall significant change in the degree of stenosis when four of these patients were examined by Doppler echocardiography six months after operation (44 (17) mm Hg), although one patient (case 5) did show a significant reduction in gradient. This patient had angiographic and echocardiographic features of dysplasia and commissural fusion. Several echographic features were common to all patients and distinguished them from cases of typical pulmonary valve stenosis. These were: *(a)* pronounced thickening of leaflets; *(b)* leaflet immobility in diastole and systole; *(c)* no dilatation of the sinuses of Valsalva in diastole, and *(d)* supra-annular narrowing.

These poor results of balloon dilatation suggest that commissural fusion is not an important mechanism for causing stenosis in the dysplastic pulmonary valve. When dysplasia of the pulmonary valve is identified clinically and echocardiographically, balloon dilatation is unlikely to improve haemodynamic function; however, it should be attempted if commissural fusion is present.

About 10% of cases of congenital heart disease have isolated pulmonary valve stenosis.[1] The mechanism of stenosis may be commissural fusion, resulting in a reduced haemodynamic orifice, or dysplasia of valve leaflets,[2–6] which presents obstruction to flow, with or without a commissural component and a hypoplastic valve annulus. Dysplasia of the pulmonary valve is often found as an associated cardiac anomaly in Noonan's syndrome.[7 8] The angiographic features of dysplasia include pronounced thickening of valve leaflets with irregular asymmetric doming in systole, little change in leaflet appearance between diastole and systole, hypoplasia of the proximal main pulmonary artery, and no radiolucent jet on cineangiocardiography.[5] Surgical experience with standard commissurotomy had been disappointing[6 9–11] and this technique has been abandoned in favour of partial or complete valve tissue resection, with or without patch enlargement of the right ventricular outflow tract.

Requests for reprints to Dr Lee N Benson, Division of Cardiology, Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.

*Department of Radiology, The Hospital for Sick Children, Toronto and Department of Radiology, University of Toronto Faculty of Medicine.

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Table 1 *Results of balloon dilatation in seven patients with dysplastic pulmonary valves*

		Pre-dilatation		*Post-dilatation*		
Patient No	*Annulus size (mm)*	*RV pressure as % of systemic*	*Gradient (mm Hg)*	*RV pressure as % of systemic*	*Gradient (mm Hg)*	*Follow up gradient (mm Hg)*
1	15	90	60	—	—	—
2	10	69	36	67	48	42
3	11	60	40	50	32	47
4	11	142	150	—	—	—
5	10·4	103	96	70	60	23
6	8	86	80	72	60	65
7	10	60	38	60	38	—
Mean (SD)	10·7(2·11)	87(29)	71·4(41·5) 58 (28)†	63·8(8·9)	47·6(12·6)	44·2(17·2)

RV, right ventricular.
†Only patients dilated.

Percutaneous balloon dilatation has now replaced open heart valvotomy for the relief of typical pulmonary valve stenosis.[12-17] The attendant morbidity is minimal and short term results appear to be good. A few patients with dysplasia of the pulmonary valve have undergone this procedure but balloon dilatation has not been specifically assessed in this condition.[14 15 17] We report our experience of using balloon dilatation in patients who had dysplasia of the pulmonary valve that was identified by cross sectional echocardiographic criteria.

Patients and methods

Seven of 38 patients undergoing percutaneous balloon dilatation of the pulmonary valve between January 1984 and December 1985 were prospectively identified as having clinical features consistent with dysplasia of the pulmonary valve. Three patients had the Noonan phenotype (cases 1, 2, and 3). None had a pulmonary ejection click. Plain chest radiographs did not reveal post-stenotic dilatation of the main pulmonary artery (a feature noted in at least 90% of patients with typical pulmonary valve stenosis[5]). The frontal QRS axis of the electrocardiogram exceeded +170° in five cases. Two patients (cases 3 and 5) had an associated patent foramen ovale.

Echocardiographic imaging was carried out with an ATL Mark 600 or Ultramark 8 mechanical sector scanner ultrasound system (Advanced Technology Laboratories Inc, Bellevue, WA). Images were obtained from the standard and high parasternal short axis views. When we simultaneously measured Doppler echocardiographic gradients and intracardiac pressures in 39 patients with pulmonary valve stenosis we obtained a good correlation (r = 0·95) (gradient (catheter) = 0·89 [gradient (echo)] + 3·98).

Angiocardiography was carried out under ketamine anaesthesia before balloon dilatation. The details of our dilatation procedure have been reported elsewhere.[18] Briefly, systemic and right ventricular pressures are continuously monitored before and during dilatation. Balloon catheters with diameters that are 20–30% greater than annulus diameter measured from the lateral right ventriculogram (table 1) are positioned across the pulmonary valve by means of a guide wire in the left pulmonary artery. Inflation-deflation cycles are rapid (less than 15 seconds) and they are repeated (usually for two or three cycles) until no waist can be identified when the balloon is inflated.

Patient 1, in whom pulmonary valve dysplasia had been identified clinically and angiocardiographically, underwent balloon dilatation at the time of surgery. Balloon size was selected according to the preoperative angiogram and the balloon was placed across the pulmonary valve ring from the pulmonary artery and inflated once after cardiopulmonary bypass had been started.

Results

Table 1 shows the results of balloon dilatation. The balloon catheter could not be passed across the pulmonary valve in one patient (case 4). In the operating room, before dilatation, patient 1 was seen to have thickened "fleshy" valve leaflets. A tear was seen in the anterior commissure of this valve as a result of dilatation. This suggests an element of commissural fusion, and in this instance the orifice increased from 3 to 10 mm according to Hegar dilator sizing.

During percutaneous balloon dilatation in the remaining five cases no waist was seen during the initial inflation cycle. Immediately after the procedure the mean pressure gradient across the pulmonary valve decreased insignificantly from 58 (28) to 47 (12) mm Hg. Doppler echocardiography in four patients (cases 2, 3, 5, and 7) six months after operation showed no overall significant relief of stenosis. One

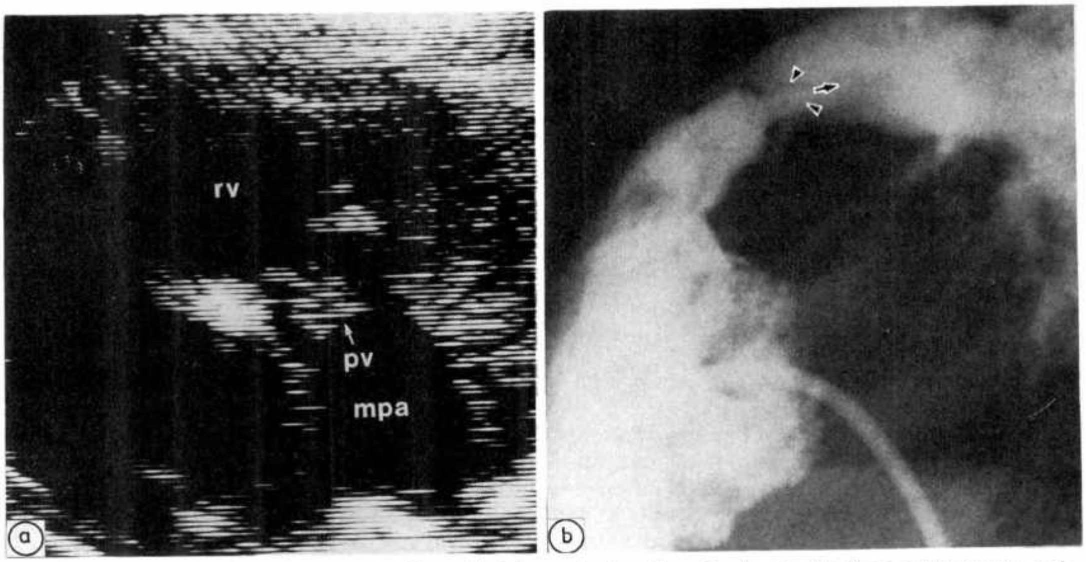

Fig 1 *Cross sectional echocardiograms. (a) Precordial short axis view of a valve showing dysplasia (white arrow) and commissural fusion. The cusp closest to the aorta appeared to be immobile during systole. The left sided cusp, however, appeared to dome during the cardiac cycle. (b) An angiocardiogram from the same patient, showing a central jet (black arrows); the valve leaflets are thickened. mpa, main pulmonary artery; pv, pulmonary valve; rv, right ventricle.*

patient (case 5), however, did have a significant reduction in gradient from 60 mm Hg immediately after dilatation to 23 mm Hg six months later (table 1). The pulmonary valve showed features of commissural fusion in addition to dysplasia. On the angiogram the base of one of the leaflets appeared to be thin and a systolic jet was noted (fig 1). An echocardiogram (fig 1) of the pulmonary valve from the long axis view showed doming as well as leaflet thickening, with widening of one of the sinuses of Valsalva in diastole. Thus although the valve leaflets were thickened, there was an element of commissural fusion to account for the success of balloon dilatation.

Table 2 shows the angiographic and echocardiographic features in these patients. All patients showed angiographic evidence of thickening of pulmonary valve leaflets. A supra-annular ridge was noted in all but one patient (case 7) (fig 2). Patients 5 and 7 did not show asymmetric systolic doming, and a systolic jet was seen in four of the seven patients. Post-stenotic dilatation of the proximal main pulmonary artery was present in two patients (cases 4 and 7). Patients 5 and 7 showed diastolic widening of one sinus of Valsalva on the lateral projection of the right ventriculogram, suggesting that in addition to dysplasia there was commissural fusion between at least two adjacent cusps. None of the patients had fixed subvalve pulmonary stenosis. The mean (SD) diameter of the pulmonary valve annulus was 10·7 (2·11) mm and this is 90 (18) % of the predicted normal for body weight.[19]

Table 2 *A comparison of angiographic and echocardiographic features in seven patients with dysplastic pulmonary valves*

	Patient No:						
	1	*2*	*3*	*4*	*5*	*6*	*7*
Angiographic features:							
Thickened leaflets	+	+	+	+	+	+	+
Asymmetrical systolic doming	+	+	+	+	○	+	○
Supra-annular narrowing	+	+	+	+	+	+	○
Systolic jet	○	○	+	+	+	○	+
Post-stenotic dilatation	○	○	○	+	○	○	+
Echocardiographic features:							
Thickened leaflets	+	+	+	+	+	+	+
Immobility of leaflets	+	+	+	+	○	+	○
Supra-annular narrowing	+	+	+	+	+	+	○
Post-stenotic dilatation	○	○	○	○	○	○	+

+, present; ○, absent.

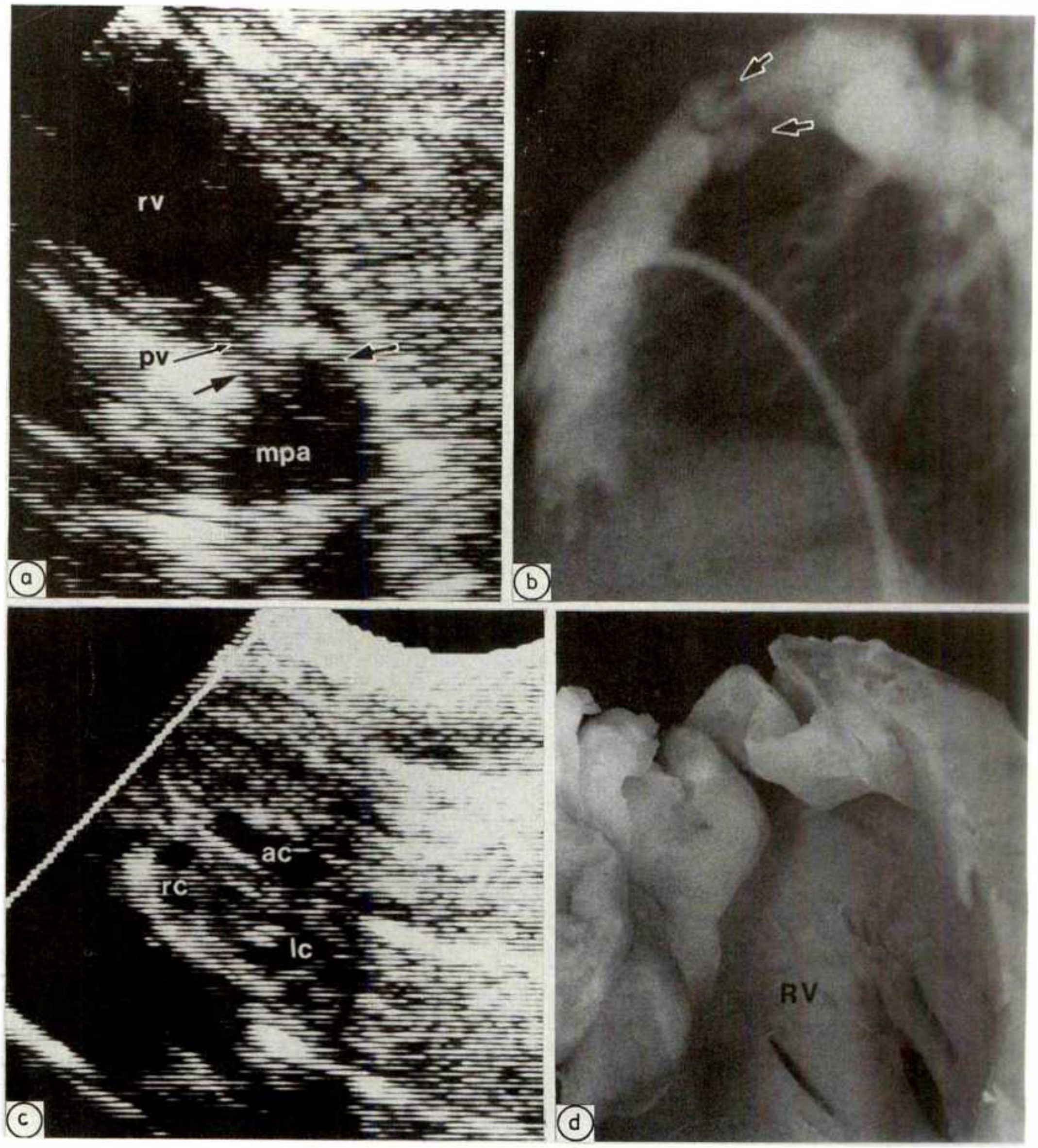

Fig 2 *(a) Echocardiogram of precordial long axis view from a patient with a dysplastic pulmonary valve. Note the bright echoes originating from the thickened valve. There is also evidence of supravalvar narrowing (black arrows). (b) Angiocardiogram in the same patient. Note the absence of a central jet, the supravalvar narrowing (black arrows), and a fleshy appearance of the valve leaflets. (c) Short axis echocardiographic view. (d) Photograph of long axis cut from another patient with a dysplastic pulmonary valve showing fleshy and thickened valve leaflets. There is no evidence of fusion along the commissures. ac, anterior cusp; lc, left cusp; rc, right cusp; mpa, main pulmonary artery; pv, pulmonary valve; rv, right ventricle.*

The cross sectional echocardiographic features that were common to patients with dysplasia correlated closely with those seen during ventriculography (figs 1–2 and table 2). The high parasternal short axis view revealed tricuspid pulmonary valves in all patients. Both the shape and the mobility of individual valve leaflets could be determined by combining the parasternal long and short axis views;

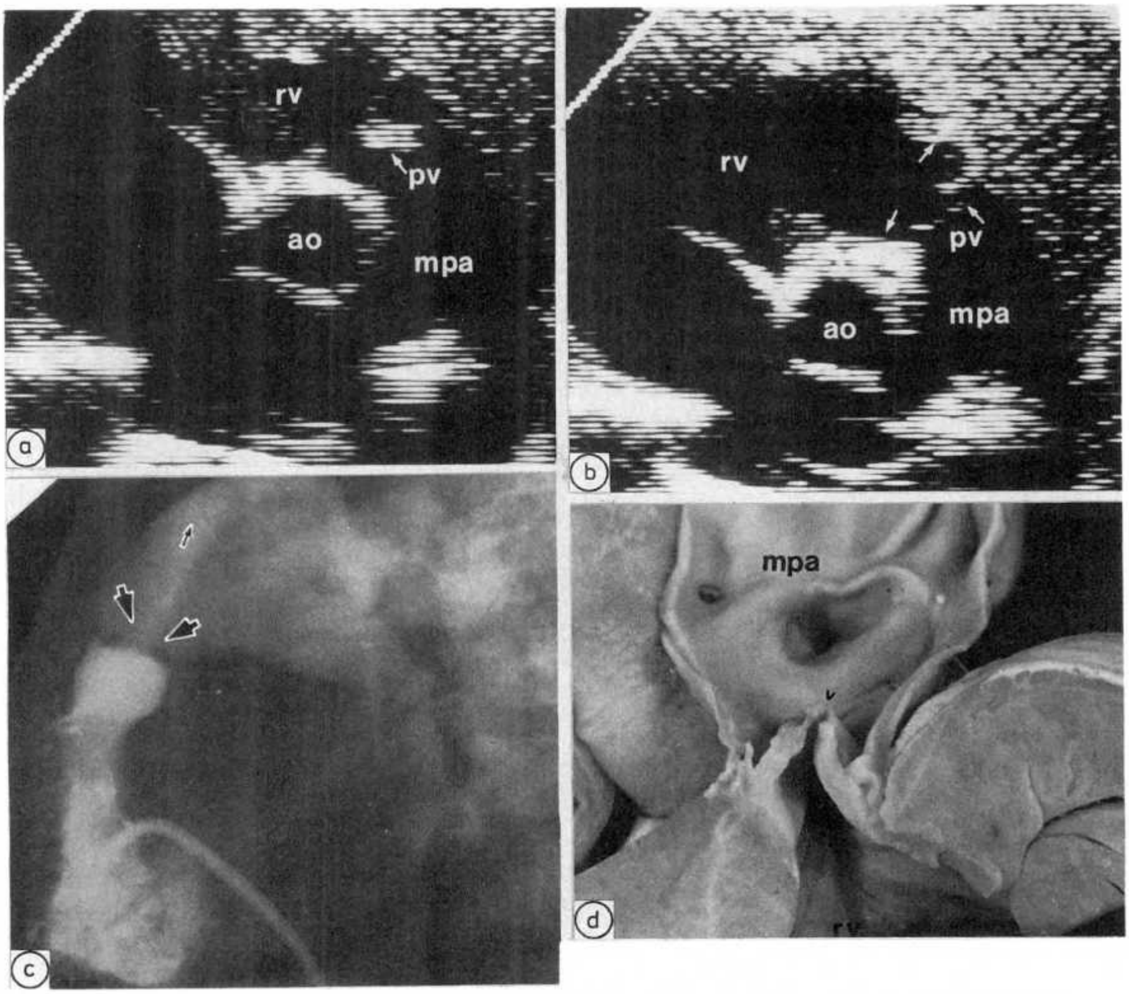

Fig 3 *(a) Echocardiogram of precordial short axis view from a patient with typical pulmonary valve stenosis. Note the bright echoes at the tips of the leaflets where the commissures fuse; the remainder of the leaflet appears to be thin. (b) Valve doming in the same patient; the white arrows indicate the margins of the valve annulus. (c) Angiocardiogram showing the central jet typical of isolated pulmonary valve stenosis. (d) Photograph of a specimen cut in the long axis from a neonate with critical pulmonary valve stenosis. Note the pinpoint orifice indicated by the black arrow. The valve leaflets are slightly thickened; however, they are very different from the fleshy leaflets in the patient with a dysplastic valve seen in fig 2. ao, aorta; mpa, main pulmonary artery, pv, pulmonary valve; rv, right ventricle.*

all patients had thickened leaflets. Poor leaflet mobility could be seen in both long and short axis views in all patients except cases 5 and 7. The anterior sinus of Valsalva in each of these patients showed diastolic widening in the parasternal long axis view—a feature not seen in either the posterior sinuses of Valsalva in these two cases or in any of the other patients. Post-stenotic dilatation of the main pulmonary artery was seen in one patient only (case 7).

Discussion

The association of a particular phenotype with pulmonary valve stenosis has been well recognised since the original description by Noonan in the early 1960s, with up to 50% of patients having dysplasia of the valve as the mechanism of stenosis.[7 8] It is very likely that the wide variation seen in the physical features of this syndrome is similarly expressed in variable degrees of valve dysplasia.[3] Other clinical features distinguishing dysplasia from typical (commissural fusion) pulmonary valve stenosis are absence of an ejection click, a frontal QRS axis of >170° on surface electrocardiogram, and lack of post-stenotic dilatation of the main pulmonary artery on the chest radiograph.[4-6 9]

The gold standard of diagnosis, however, remains the angiographic demonstration of considerably thickened valve leaflets, irregular asymmetrical doming in systole, absence of diastolic widening of sinuses of Valsalva, and a hypoplastic valve annulus and proximal main pulmonary artery.[5] Furthermore, a systolic contrast jet is occasionally seen. On the basis of necropsy examinations,[4] the mechanism of obstruction is thought to result from the thickening of the leaflets, which are confined within a hypoplastic valve annulus, with little or no commissural fusion.[4 6 9] The echocardiographic features for the diagnosis of pulmonary valve dysplasia correlate well with the angiographic features. They are pronounced leaflet thickening combined with lack of diastolic widening of the sinuses of Valsalva and supra-annular narrowing. Poor mobility of pulmonary valve leaflets was seen in both the parasternal long and high short axis views. Evidence of diastolic widening of one or more of the sinuses of Valsalva in the long axis view suggests that commissural fusion, as well as a leaflet abnormality, may be a part of the mechanism of obstruction. These observations are in direct contrast with those seen in typical isolated pulmonary valve stenosis in which the mechanism of stenosis is commissural fusion (fig 3).

The application of balloon dilatation to dysplasia of the pulmonary valve was disappointing in our series and in the five patients reported by other investigators.[14 15 17] This is not surprising because disruption of commissural fusion appears to be the mechanism for relief of obstruction in this condition.[18] Valve annulus hypoplasia cannot account for residual or persistent stenosis because hypoplasia (that is <2SD below expected normal) was not a prominent feature in our patients, although this feature was noted by others.[2-6] Furthermore, among patients with pulmonary valve stenosis, there will be a number with mixed dysplasia and commissural fusion. It is of interest that 20% of patients with valve dysplasia described by Jeffrey *et al*, showed angiographic systolic jetting,[5] a feature found in >90% of cases of typical doming pulmonary valve stenosis. Similarly Schneeweiss *et al* discussed 12 anatomically confirmed cases of pulmonary valve dysplasia and showed post-stenotic dilatation in 75% and systolic jetting in 33%.[20] The traditional angiographic features of pulmonary valve dysplasia may therefore reflect some contribution by commissural fusion.

Patients with mixed commissural fusion and dysplasia may obtain relief of stenosis from balloon dilatation of the valve. Cross sectional echocardiographic imaging of the pulmonary valve, particularly in the parasternal long axis view, allows adequate imaging of at least two of the leaflets (figs 1 and 3). Where echocardiographic imaging demonstrates features suggestive of dysplasia, diastolic frames should be carefully examined for widening of the sinuses of Valsalva. This feature we believe indicates that commissural fusion is part of the mechanism of obstruction. In those instances, cardiac catheterisation and angiography should be undertaken to confirm the presence of commissural fusion and dysplasia and balloon dilatation should be considered when gradient reduction is regarded as clinically appropriate.

References

1 Campbell M. Simple pulmonary stenosis. Pulmonary vascular stenosis with a closed ventricular septum. *Br Heart J* 1954;16:273–300.

2 Noonan JA Hypertelorism with Turner phenotype. *Am J Dis Child* 1968,116:373–80.

3 Linde LM, Turner SW, Sparkes RS. Pulmonary valvular dysplasia. A cardiofacial syndrome. *Br Heart J* 1973;35.301–4.

4 Koretzky ED, Moller JH, Korns ME, Schwartz CJ, Edwards JE. Congenital pulmonary stenosis resulting from dysplasia of the valve. *Circulation* 1969, 40:43–53.

5 Jeffrey RF, Moller JH, Amplatz K. The dysplastic pulmonary valve: a new roentgenographic entity. *Am J Roentgenol Rad Therapy Nuclear Med* 1972;114: 322–39.

6 Schieken RM, Friedman S, Pierce WS. Severe congenital pulmonary stenosis with pulmonary valvular dysplasia syndrome. *Ann Thorac Surg* 1973;15· 570–7.

7 Duncan WJ, Fowler RS, Farkas LG, *et al.* A comprehensive scoring system for evaluating Noonan syndrome. *Am J Med Genet* 1981;10:37–50.

8 Nora JJ, Nora AH, Sinha AK, Spangles RD, Lubs HA. The Ullrich-Noonan syndrome (Turner phenotype). *Am J Dis Child* 1974;127:48–55.

9 Watkins L Jr, Donahoo JS, Harrington D, Haller JA, Neill CA. Surgical management of congenital pulmonary valve dysplasia. *Ann Thorac Surg* 1977; 21:498–507.

10 Mistrot J, Neal W, Lyons G, *et al.* Pulmonary valvulotomy under inflow stasis for isolated pulmonary stenosis. *Ann Thorac Surg* 1976;21:30–7.

11 Vancini M, Roberts KD, Silove ED, Singh SP. Surgical treatment of congenital pulmonary stenosis due to dysplastic leaflets and small valve annulus. *J Thorac Cardiovasc Surg* 1980;79:464–8.

12 Kan JS, White RI Jr, Mitchell SE, Gardner TJ.

Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary valve stenosis. *N Engl J Med* 1982;**307**:540–2.

13 Labadidi Z, Jiunn-Ren W. Percutaneous balloon pulmonary valuloplasty. *Am J Cardiol* 1983,**52**:560–2.

14 Kan JS, White RI Jr, Mitchell SE, Anderson JH, Gardner TJ. Percutaneous transluminal balloon valvuloplasty for pulmonary valve stenosis. *Circulation* 1984;**69**:554–60.

15 Walls JT, Labadidi Z, Curtis JJ, Silver D Assessment of percutaneous balloon pulmonary and aortic valvuloplasty. *J Thorac Cardiovasc Surg* 1984,**88**:352–6.

16 Rocchini AP, Kveselis DA, Crowley D, Dick M, Rosenthal A. Percutaneous balloon valvuloplasty for treatment of congenital pulmonary valvular stenosis in children. *J Am Coll Cardiol* 1984;**3**:1005–12.

17 Tynan M, Baker EJ, Rohmer J, *et al.* Percutaneous balloon pulmonary valvuloplasty. *Br Heart J* 1985; **53**:520–4.

18 Benson LN, Smallhorn JS, Freedom RM, Trusler GA, Rowe RD Pulmonary valve morphology after balloon dilatation of pulmonary valve stenosis. *Cathet Cardiovasc Diagn* 1985;**11**:161–6.

19 Rowlatt VF, Rimoldi HJA, Lev M. The quantitative anatomy of the normal child's heart. *Pediatr Clin N Am* 1963;**10**:499.

20 Schneeweiss A, Blisden LC, Shem-Tov A, Orr D, Milo S, Neufeld HN. Diagnostic angiocardiographic criteria in dysplastic pulmonic valve. *Am Heart J* 1985;**106**:761–2.

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Thrombocytopenia in patients with aortopulmonary transposition and an intact ventricular septum

MASARU TERAI, MAKOTO NAKAZAWA, ATSUYOSHI TAKAO,
YASUHARU IMAI

From the Departments of Paediatric Cardiology and Paediatric Cardiovascular Surgery, The Heart Institute of Japan, Tokyo Women's Medical College, Tokyo, Japan

SUMMARY Relations between platelet counts and mean pulmonary arterial pressures, capillary oxygen tension, and haematocrit were studied in 37 patients, aged 2 to 16 months, with simple aortopulmonary transposition (an intact ventricular septum and no ductus arteriosus). There was a statistically significant inverse relation between pulmonary arterial pressures and platelet counts. Six out of the eight patients (4–16 months old) with raised mean pulmonary arterial pressure had thrombocytopenia ($<100\,000/mm^3$) and none of the 25 patients with a normal mean pulmonary pressure ($\leqslant 20$ mm Hg) showed thrombocytopenia. Pulmonary arterial pressures were not measured in four patients: the platelet count was $7000/mm^3$ in the patient with a left ventricular systolic pressure of 90 mm Hg but it was $>100\,000/mm^3$ in the three in whom left ventricular systolic pressure was <50 mm Hg. Platelet counts were positively correlated with capillary oxygen tension and inversely correlated with haematocrit in all 37 patients. Despite the persistence of pulmonary hypertension, thrombocytopenia improved after corrective surgery in five patients, even in those who had thrombocytopenia before operation.

These data suggest that the presence of thrombocytopenia is not solely related to the development of pulmonary vascular disease. Pulmonary vascular disease, however, does contribute to the early development of thrombocytopenia in patients with simple aortopulmonary transposition.

Haematological abnormalities including polycythaemia, thrombocytopenia, and hypercoaguability are often reported in patients with cyanotic heart disease.[1–3] These abnormalities can cause serious perioperative complications. Although some studies have indicated that patients with cyanotic heart disease may have disseminated intravascular coagulation[4–6] others have not.[2 7]

We have found severe thrombocytopenia with a bleeding tendency in some of our patients with simple aortopulmonary transposition (an intact ventricular septum and no ductus arteriosus) in whom pulmonary arterial pressure is raised. This prompted an investigation of the association of thrombocytopenia and pulmonary hypertension in patients with simple aortopulmonary transposition.

Patients and methods

We studied 37 consecutive patients (aged 2–16 months (mean 8)) with simple aortopulmonary transposition who underwent preoperative cardiac catheterisation at our hospital between January 1979 and March 1985. Patients with a ductus arteriosus were excluded from the study.

Pulmonary arterial pressure was measured in 33 patients, and in these patients we studied the interrelation between platelet counts and mean pulmonary arterial pressures. We also studied the relations between platelet counts and the capillary oxygen tension or haematocrit value in 37 patients, including the four patients in whom pulmonary arterial pressures were not measured. The platelet count was obtained with a Coulter Thrombocounter at the time of preoperative haemodynamic assessment. When thrombocytopenia was found we used the Rees-Ecker method to confirm the count. A

Requests for reprints to Dr Makoto Nakazawa, Department of Paediatric Cardiology, The Heart Institute of Japan, Tokyo Women's Medical College, 10 Kawada-cho, Shinjuku, Tokyo 162, Japan.

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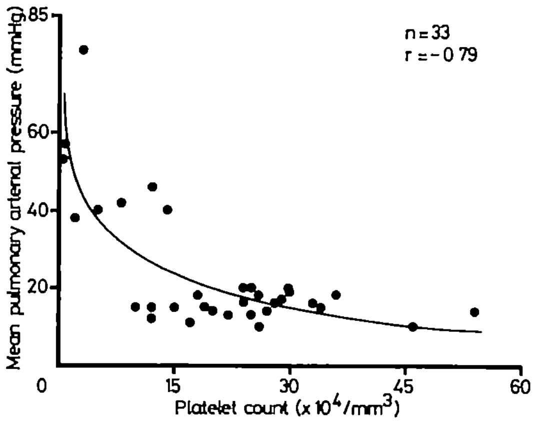

Fig 1 *Inverse correlation between platelet counts and mean pulmonary arterial pressure. This relation is non-linear; the best fit is obtained with the logarithmic function* *($r = -0{\cdot}79, p < 0\ 001$).*

platelet count of $< 100\,000/\text{mm}^3$ was regarded as showing thrombocytopenia.

Correlations between the platelet count and the mean pulmonary arterial pressure, capillary oxygen tension, and haematocrit were tested by regression analysis with simple linear or logarithmic equations.

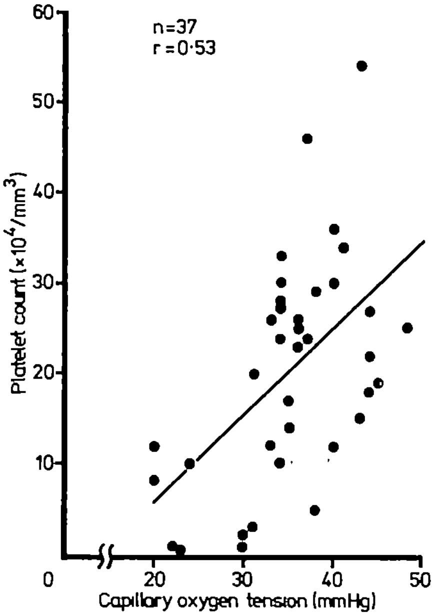

Fig 2 *Relation between platelet counts and capillary oxygen tension ($r = 0{\cdot}53, p < 0{\cdot}01$).*

Results

RELATIONS BETWEEN PLATELET COUNTS AND MEAN PULMONARY ARTERIAL PRESSURES, CAPILLARY OXYGEN TENSION, AND HAEMATOCRIT

In the 33 patients in whom pulmonary arterial pressures were known, platelet counts were inversely correlated with mean pulmonary arterial pressures (mean pulmonary arterial pressure $= 57 - 12{\cdot}3 \log_e$ (platelet counts/10^4); $r = -0{\cdot}79$, $p < 0{\cdot}001$ (fig 1)). For example, six of the eight patients with raised mean pulmonary arterial pressure had thrombocytopenia ($< 100\,000/\text{mm}^3$). The other two patients with a raised pulmonary pressure had platelet counts of $120\,000/\text{mm}^3$ and $140\,000/\text{mm}^3$. None of the 25 patients with a normal mean pulmonary arterial pressure ($\leqslant 20$ mm Hg) was thrombocytopenic.

In the four patients in whom pulmonary arterial pressures were not measured the platelet count was $7000/\text{mm}^3$ in a patient (case 7 in table) with a left ventricular systolic pressure of 90 mm Hg and $> 100\,000/\text{mm}^3$ in the three patients in whom left ventricular systolic pressure was < 50 mm Hg.

Platelet counts were also related to capillary oxygen tension ($r = 0{\cdot}53$, $p < 0{\cdot}01$) and inversely to the haematocrit ($r = -0{\cdot}71$, $p < 0{\cdot}01$) in all 37 patients (figs 2 and 3).

CLINICAL CHARACTERISTICS IN PATIENTS WITH THROMBOCYTOPENIA

Seven (19%) of the 37 patients were thrombocytopenic. The table summarises the clinical features. Their ages at catheterisation ranged from four

Table *Characteristics of thrombocytopenic patients*

		Before surgery					*After surgery*	
Case No	*Age (mnth)*	*Platelets ($\times 10^4/mm^3$)*	*Po_2 (mm Hg)*	*Haematocrit (%)*	*MPAP (mm Hg)*	*Surgery*	*Platelets ($\times 10^4/mm^3$)*	*MPAP (mm Hg)*
1	11	2	30	60	38	Senning	22	78
2	16	1	22	62	57	Senning	21	ND
3	4	8	20	63	42	PAB, BT	1	67
4	12	0 6	23	65	53	Senning	23	ND
5	12	3	31	61	81	Senning	39	67
6	15	5	38	73	40	Jatene	19	29
7	12	0·7	30	66	ND	Jatene	4	83

Po_2, capillary oxygen tension; MPAP, mean pulmonary artery pressure; PAB, pulmonary artery banding; BT, Blalock-Taussig shunt; ND, not done.

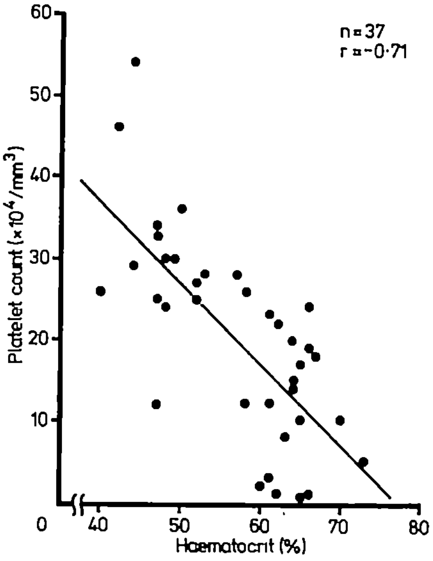

Fig 3 *Inverse relation between platelet counts and haematocrit* $(r = -0{\cdot}71, p < 0{\cdot}01)$.

to 16 months and five of them were between 12 and 16 months old.

Five patients who had a platelet count of $< 30\,000/mm^3$ showed haemorrhagic complications such as generalised petechiae or purpura and haematuria. Bone marrow aspiration in three patients showed adequate numbers of megakaryocytes with normal platelet production in all of them.

Six patients (cases 1–6) had raised mean pulmonary arterial pressures (38–81 mm Hg) before operation. The thrombocytopenic ($7000/mm^3$) patient (case 7) in whom the pulmonary arterial pressure was not measured had a left ventricular systolic pressure of 90 mm Hg. In this case no pulmonary stenosis was found at operation.

After catheterisation all seven patients underwent operation: a Senning operation in four, a Jatene procedure with a Lecompte modification in two, and pulmonary arterial banding with Blalock-Taussig shunt in one. Pulmonary arterial pressure was measured in five of them one day to four years after operation. Mean pulmonary arterial pressure had not fallen to normal (≤ 20 mm Hg) in any of them. One patient (case 7) died of pulmonary vascular obstruction eight days after operation.

In all six survivors the postoperative platelet count increased to normal within 30 days after operation. In one patient (case 3) who had undergone palliative surgery, however, hypoxaemia developed five months after operation; thrombocytopenia progressed when the mean pulmonary arterial pressure reached 67 mm Hg.

Discussion

Thrombocytopenia develops gradually in patients with cyanotic heart disease.[7-9] Ekert *et al* reported platelet counts of $< 100\,000/mm^3$ in eight of 28 patients with cyanotic heart diseases, including aortopulmonary transposition; all eight were more than three years old.[7] Paul *et al* showed that thrombocytopenia was rare in infants aged less than a year.[9] Gross *et al* showed that thrombocytopenia was most common in older patients with hypoxaemia and polycythaemia.[8] Thus it seems likely that the severity of thrombocytopenia in patients with cyanotic heart disease is related to the duration of both hypoxaemia and polycythaemia. The present study also showed that the severity of hypoxaemia and polycythaemia was significantly related to the platelet count. Some investigators have demonstrated a decrease in platelet life span in cyanotic patients with normal platelet counts as well as in those with thrombocytopenia,[10,11] suggesting that there may be compensated thrombocytolysis with relative and absolute megathrombocytosis in cyanotic patients.

In our patients with simple aortopulmonary transposition thrombocytopenia was even found in patients aged less than 18 months if pulmonary arterial pressure was increased. In addition, continuing high pulmonary arterial pressures in these patients after corrective surgery indicated the presence of pulmonary vascular obstructive disease. The early occurrence of thrombocytopenia associated with advanced pulmonary vascular disease may be a specific feature of simple aortopulmonary transposition.

It is now generally thought that pulmonary vasoconstriction caused by hypoxaemia, a high haematocrit, and increased pulmonary blood flow may increase the shear stress on the endothelium and cause endothelial damage. Platelets aggregate at such sites. All three factors occur in simple aortopulmonary transposition and this may explain the rapid progression of pulmonary vascular disease in such patients.[12] Wagenvoort *et al* in their histological study of patients with simple aortopulmonary transposition showed that the pulmonary arteries had thin walls and wide lumens, especially in patients with high haematocrits.[13] Moreover, they found intimal fibrosis indicative of organised thrombi in some of their patients. Pulmonary thrombi contribute to further progressive vascular disease.[14] An association of pulmonary vascular disease and thrombocytopenia has not been established, however.

As we have shown, corrective surgery resulting in increased oxygen saturation can increase platelet counts in patients with severe thrombocytopenia before operation, despite the persistence of pulmonary hypertension. Clearly the presence of thrombocytopenia is not solely related to the development of pulmonary vascular disease. The pulmonary vascular state may, however, influence the rate of destruction of platelets in the lung. In other words the association of pulmonary vascular disease may contribute to the early induction of thrombocytopenia in patients with simple aortopulmonary transposition.

Although the basic mechanism has not been confirmed, thrombocytopenia is an important clinical finding which indicates the presence or development of pulmonary vascular disease. Operation during early infancy should prevent the development of pulmonary vascular disease and haematological abnormalities.

References

1 Iolster NJ. Blood coagulation in children with cyanotic congenital heart disease. *Acta Paediatr Scand* 1970;**59**:551–7

2 Wedemeyer AL, Edson JR, Krivit W. Coagulation in cyanotic congenital heart disease. *Am J Dis Child* 1972;**124**:656–60.

3 Wedemeyer AL, Lewis JH. Platelet survival studies in cyanotic cardiac patients [Abstract]. *J Pediatr* 1973,**83**:161.

4 Dennis LH, Stewart JL, Conrad ME. Heparin treatment of haemorrhagic diathesis in cyanotic congenital heart disease. *Lancet* 1967;**i**:1088–9.

5 Komp DM, Sparrow AW. Polycythemia in cyanotic heart disease—a study of altered coagulation. *J Pediatr* 1970;**76**:231–6.

6 Ihenacho HNC, Breeze GR, Fletcher DJ, Stuart J. Consumption coagulopathy in congenital heart-disease. *Lancet* 1973;**i**:231–4.

7 Ekert H, Gilchrist GS, Stanton R, Hammond D. Hemostasis in cyanotic congenital heart disease. *J Pediatr* 1970;**76**:221–30.

8 Gross S, Keefer V, Liebman J. The platelets in cyanotic congenital heart disease. *Pediatrics* 1968; **42**:651–8.

9 Paul MH, Currimbhoy Z, Miller RA, Schulman I. Thrombocytopenia in cyanotic congenital heart disease [Abstract]. *Circulation* 1961;**24**:1013.

10 Waldman JD, Czapek EE, Paul MH, Schwartz AD, Levin DL, Schindler S. Shortened platelet survival in cyanotic heart disease. *J Pediatr* 1975;**87**:77–9.

11 Goldschmidt B, Sarkadi B, Gardos G, Matlary A. Platelet production and survival in cyanotic congenital heart disease. *Scand J Haematol* 1974; **13**:110–5.

12 Aziz KU, Paul MH, Rowe RD. Bronchopulmonary circulation in d-transposition of the great arteries. Possible role in genesis of accelerated pulmonary vascular disease. *Am J Cardiol* 1977;**39**:432–8.

13 Wagenvoort CA, Nauta J, van der Schaar PJ, Weeda HWH, Wagenvoort N. The pulmonary vasculature in complete transposition of the great vessels, judged from lung biopsies. *Circulation* 1968;**38**:746–54.

14 Newfeld EA, Paul MH, Muster AJ, Idriss FS. Pulmonary vascular disease in transposition of the great vessels and intact ventricular septum. *Circulation* 1979;**59**:525–30.

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Case reports

Myocardial infarction caused by coronary artery damage from blunt chest injury

S D PRINGLE, K G DAVIDSON

From the Departments of Medical Cardiology and Cardiothoracic Surgery, Royal Infirmary, Glasgow

SUMMARY A case is reported in which blunt chest injury caused an intimal tear in the left anterior descending coronary artery. Despite few external signs of injury the patient sustained a myocardial infarction resulting in life threatening arrhythmias and considerable left ventricular dysfunction.

Chest trauma is a rare but important cause of cardiac damage. It most commonly results from steering wheel injuries in road traffic accidents[1] but has also been reported in physical assaults[2] and as a result of sporting injuries.[3] Direct injury may cause cardiac rupture, ventricular septal defect, and valvar or myocardial damage.[4] Less commonly the coronary arteries may be injured. We report a case of anterior myocardial infarction occurring after damage to the intima of the left anterior descending coronary artery.

Case report

A 20 year old man was admitted to Monklands District General Hospital after a road traffic accident. He had been found wandering confused near his motorcycle which had been in collision with a lamp standard. On arrival at hospital he was fully conscious but disorientated. He had abrasions to his face and right arm, bruising of his anterior chest wall, and a fractured right clavicle. Heart rate was 80 beats/min and blood pressure was 130/90 mm Hg. One hour after admission he developed severe retrosternal pain associated with nausea and sweating. He became hypotensive with a blood pressure of 90/60 mm Hg. An electrocardiogram showed ST elevation in leads V1–V4 consistent with an anteroseptal myocardial infarction. He was transferred to the coronary care unit where electrocardiographic monitoring demonstrated several episodes of non-sustained ventricular tachycardia. The next day he developed bifascicular block with right bundle branch block and left anterior hemiblock, which progressed to complete heart block requiring temporary transvenous pacing. Echocardiography demonstrated a dilated left ventricle with akinesis of the septum but no pericardial effusion.

Over the next two days the conduction defects resolved and he made an uncomplicated recovery. Substantial myocardial damage was confirmed by a considerable increase in serum creatine kinase (9944 U/l). Cardiac catheterisation six weeks after the accident demonstrated impaired ventricular function with a large anterior akinetic area and a left ventricular end diastolic pressure of 25 mm Hg. Selective arteriography demonstrated a severe intimal tear of the left anterior descending coronary artery at its origin (figure). The other coronary arteries were normal.

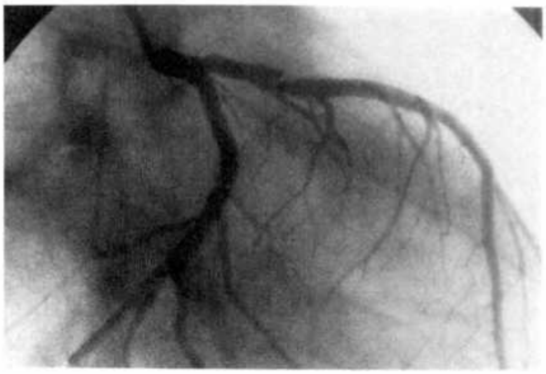

Figure *Selective arteriography of the left coronary artery showing an intimal tear of the proximal left anterior descending coronary artery.*

Requests for reprints to Dr S D Pringle, Department of Medical Cardiology, Royal Infirmary, Glasgow G31 2ER.

Discussion

The heart's position between the sternum and the vertebral column makes it liable to injury from non-penetrating chest trauma. This may be more common than previously thought. Non-invasive techniques such as radionuclide angiography have demonstrated cardiac damage in up to 55% of patients with blunt chest trauma.[5] Most cardiac injuries are the result of direct trauma to the myocardium causing concussion or contusion. A recent study has suggested that the differentiation between concussion and contusion may be important because the risk of ventricular arrhythmias is increased by contusion.[6]

In addition to direct injury, myocardial infarction may occur as a consequence of damage to the coronary arteries causing lesions ranging in severity from coronary artery rupture and fistula formation to atheromatous plaque fissuring and intimal tears.[7] These injuries are much less common, accounting for 10 out of 548 patients in one series of fatal chest trauma[8] and only one out of 258 cases in a prospective study of non-penetrating chest trauma.[9] Two of these 11 injuries were intimal tears of previously normal arteries. In most previous reports of angiographically proven coronary artery injury in non-fatal chest trauma[10 11] there has been total occlusion of the damaged artery. The assumption is that intimal damage with subsequent thrombotic occlusion occurred. In the presence of a total occlusion, however, it is difficult to be certain about underlying intimal damage. In the two reports in which the artery was not occluded, one had atheroma elsewhere in the coronary tree and this suggests that atheromatous plaque fissuring was the most likely underlying cause.[3] The other case demonstrated a non-occluded intimal lesion in an otherwise normal right coronary artery.[12]

The case reported here is of a non-occlusive intimal tear in an otherwise normal left anterior descending coronary artery. The intimal lesion itself may have been responsible for the myocardial infarction by causing mechanical obstruction or by inducing local spasm; a more likely explanation is that there was a superadded thrombotic occlusion that had undergone thrombolysis during the interval between infarction and angiography. Traumatic induction of fissuring in an atheromatous plaque seems unlikely in such a young person with an otherwise normal coronary artery tree.

In our patient there were few signs of trauma to the chest and yet he sustained a myocardial infarction with considerable left ventricular damage. As in previous studies,[6 13] echocardiography was useful in providing evidence of myocardial damage. The importance of early recognition is emphasised by this case in which there were life threatening arrhythmias and conduction abnormalities that required prompt treatment.

There should be a high index of suspicion of cardiac injury in all cases of non-penetrating chest trauma even when there are relatively trivial external signs of injury. All such patients should have an electrocardiogram as part of their initial assessment; if this shows changes consistent with myocardial injury we recommend further assessment by echocardiography.

We thank Dr A J S Gardiner and Dr I Hutton for permission to report this case.

References

1 Bancewicz J, Yates D. Blunt injury to the heart. *Br Med J* 1983;**186**:497–8.
2 Oren A, Bar-Shzomo B, Stern S. Acute coronary occlusion following blunt injury to the chest in the absence of coronary atherosclerosis. *Am Heart J* 1976;**92**:501–5.
3 Watt AH, Stephens MR. Myocardial infarction after blunt chest trauma incurred during rugby football that later required cardiac transplantation. *Br Heart J* 1986;**55**:408–10.
4 Tengler ML. The spectrum of myocardial trauma. *J Trauma* 1985;**25**:620–7.
5 Sutherland GR, Driedger AA, Holiday RL, Cheung HW, Sibbald WJ. Frequency of myocardial injury after blunt chest trauma as evaluated by radionuclide angiography. *Am J Cardiol* 1984;**52**:1099–103.
6 Frazee RC, Mucha P, Farnell MB, Miller FA. Objective evaluation of blunt cardiac trauma. *J Trauma* 1986;**26**:510–20.
7 Allen RP, Liedtke AJ. The role of coronary artery injury and perfusion in the development of cardiac contusion secondary to non penetrating chest trauma. *J Trauma* 1979;**19**:153–6.
8 Parmley LF, Manion WC, Mattingly TW. Non-penetrating traumatic injury of the heart. *Circulation* 1958;**18**:371–96.
9 Mayfield W, Hurley EJ. Blunt cardiac trauma. *Am J Surg* 1984;**148**:162–7.
10 Pifarre R, Grieco J, Garibaldi A, Sullivan HJ, Montoya A, Bakhous M. Acute coronary artery occlusion secondary to blunt chest trauma. *J Thorac Cardiovasc Surg* 1982;**83**:122–5.
11 Stern T, Wolf RY, Reichart B, Harrington OB, Crosby VG. Coronary artery occlusion resulting from blunt trauma. *JAMA* 1974;**230**:1308–9.
12 Oliva PB, Hilgenberg A, McElroy D. Obstruction of the proximal right coronary artery with acute inferior infarction due to blunt chest trauma. *Ann Intern Med* 1979;**91**:205–7.
13 Miller SA, Seward JB, Gersh BJ, Tajik A, Mucha P. Two dimensional echo findings in cardiac trauma. *Am J Cardiol* 1982;**50**:620–7.

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Traumatic combined valve lesions with aneurysm of the sinus of Valsalva causing late onset of heart failure

SUGATO NAWA, KANAME KUROZUMI, SHIGERU TERAMOTO

From the Second Department of Surgery, Okayama University Medical School, Okayama, Japan

SUMMARY A 23 year old man was operated on because severe incompetence of the aortic, mitral, and tricuspid valve caused congestive heart failure five months after a violent steering wheel injury. The following abnormalities were found at operation: a disrupted right coronary cusp, a torn chorda of the anterior mitral leaflet, a dilated tricuspid annulus, and an intimal tear on the aortic root near the right coronary ostium that had developed into an aneurysm of the sinus of Valsalva.

Case report

A healthy 23 year old man met with a traffic accident in July 1985. The steering wheel compressed his chest and he lost consciousness for a few minutes. He was admitted to a local orthopaedic hospital with sternal pain. During a two week stay in hospital he had no symptoms of cardiac tamponade, pneumothorax, or haemothorax. Five months after the accident, however, severe congestive heart failure developed. He was referred to another local hospital; when digoxin and diuretic treatment did not improve his symptoms he was referred to our hospital. We do not know whether the heart murmur was audible when he was discharged by the orthopaedic hospital.

CLINICAL FINDINGS

Diastolic pressure in both arms was low (26 mm Hg). On auscultation grade 4/6 systolic and diastolic murmurs of a to and fro type were heard in the aortic region, radiating to both carotid arteries in systole. A grade 3/6 systolic regurgitant murmur was also heard at the apex, radiating to the axilla and spine. A pulsatile liver was palpable 7 cm below the right costal margin. A chest radiograph showed a cardiothoracic ratio of 0·68. Laboratory studies were normal.

Cross sectional echocardiography showed pronounced dilatation of the four cardiac chambers, and moderate depression of left ventricular functions (ejection fraction 54%, per cent fibre shortening 29%, and mean circumferential fibre shortening 0·97 circ/s). Echocardiography also demonstrated a severe deformity of three aortic cusps and poor coaptation of the mitral leaflets near to the posteromedial commissure. Pulsed Doppler examination showed severe to moderate regurgitant flow across the tricuspid, mitral, and aortic valves.

Cardiac catheterisation had been carried out at the referring hospital; it had demonstrated moderately raised pressure in the right ventricle (55/4 mm Hg) and in the main pulmonary artery (58/33 mm Hg). Monoplane left ventricular and aortic root contrast cineangiograms obtained by the referring hospital showed severe (3/4) aortic and mitral regurgitation. The quality of the cineangiograms was very poor. Uneven opacity of the aortic root was seen in the aortogram, but echocardiography and pulsed Doppler examination detected no further abnormality.

On the basis of these data open heart surgery was planned. Further invasive examination was not proposed because there had been cardiac decompensation immediately after cardiac catheterisation.

FINDINGS AND PROCEDURES AT OPERATION

The tricuspid annulus was markedly dilated but it had not been damaged. Careful examination of the mitral complex through the atrial septotomy showed a torn chorda and a thickened flailed area on the anterior mitral leaflet near to the posteromedial

Requests for reprints to Dr Sugato Nawa, The 2nd Department of Surgery, Okayama University Medical School, Shikata-cho 2-5-1, Okayama, Japan 700.

commissure. This lesion caused incompetence of the mitral valve. Moreover, in addition to the considerable deformity of the left and non-coronary cusps of the aortic valve, the right coronary cusp was severely disrupted. This cusp was lacerated at the bottom and only the bilateral commissural portions remained attached to the aorta. There was an intimal tear (1·0 cm long) in the right coronary sinus that was floored with old blood clots.

The tear was approximated with buttressed sutures and the severely disrupted aortic valve was replaced by a mechanical prosthetic valve (Omniscience, 25 mm). The torn mitral chorda was reimplanted into a neighbouring chorda and mitral annuloplasty was performed on the posteromedial commissure by the unilateral Kay's technique.[1] The dilated tricuspid annulus was corrected by De Vega's method.[2]

The patient survived the operation and his postoperative course was uneventful. Cardiac catheterisation after operation showed that the pressure in the right ventricle had fallen to 23/2 mm Hg and pressure in the main pulmonary artery to 26/11 mm Hg. The area-length method also showed a reduction in end diastolic and end systolic volume indices of 147 and 79 ml/m^2 from the preoperative values of 302 and 173 ml/m^2 respectively. Postoperative echocardiography showed similar reductions in left heart dimensions and an improved cardiac function. Postoperative cineangiography demonstrated excellent re-establishment of tricuspid, mitral, and aortic valve competences. Unfortunately it was only at this stage that the aneurysm of the right coronary sinus of Valsalva was apparent. It had been overlooked preoperatively.

Discussion

Important cardiac trauma occurs in 10% to 20% of the victims of fatal motor vehicle accidents.[3] The symptoms of cardiac injuries may be fulminant or delayed, occurring hours, days, and sometimes even years after the injury.[4] We do not know when incompetence of the aortic and mitral valves developed in the present case. We do not know what the findings at auscultation were when the patient was examined before discharge from the orthopaedic hospital, when the heart size and shape appeared to be normal. The laceration of the right coronary cusp and the intimal tear in the same sinus of Valsalva suggest that aortic valve incompetence was caused by injury. The aortic wall and valve injuries in this case are typical of damage caused by a water hammer phenomenon. We cannot be certain that tearing of the chorda in the mitral apparatus occurred when the aortic valve and sinus of Valsalva were disrupted. We think that damage to both the mitral and aortic valves is likely to have been caused by the impact of the steering wheel. A pathophysiological mechanism has been proposed to explain the occurrence of mitral damage,[4 5] and Kissane *et al* have described mitral regurgitation after external chest injury in dogs.[6]

We believe that the tricuspid regurgitation was a secondary effect of severe volume overload of the left heart; apart from dilatation of the annulus we found no signs of injury to the tricuspid valve. Secondary tricuspid incompetence is often associated with more conventional acquired valve disease.

Cardiovascular injuries have been reported after chest injury[4 5 7 8]; but these reports do not include cases in which operation was needed for traumatic combined valve regurgitation with aortic root intimal tear causing aneurysm of the sinus of Valsalva. Cuadros *et al* reported a similar case in which there was mitral regurgitation caused by partial laceration of papillary muscle, circumferential laceration of the aortic root, and rupture of the pericardium,[4] but in their case there was no aortic regurgitation or sinus aneurysm.

The aneurysm of the sinus of Valsalva was overlooked preoperatively because only a poor quality aortic root angiogram in the right anterior oblique projection was available from the local hospital. The very faint abnormal silhouette of the aneurysm was masked by the contrast in the aortic root. The lesion was missed on preoperative cross sectional echocardiography because abnormal anteriorly projected echoes from the aortic root were erroneously interpreted as ghost echoes. The simple approximation of torn intimal edges with buttressed sutures was not sufficient to achieve complete closure of the aneurysmal lesion, and a postoperative cineangiogram clearly showed the residual aneurysm.

We intend to monitor this residual lesion by serial cross sectional echocardiographic studies.[9] A second operation may be inevitable.[9 10]

The resected aortic cusp showed no evidence of inflammation; however, the lacerated right coronary cusp showed myxoid degeneration, almost complete absence of elastic fibres, and cystic degeneration. The mitral valve complex was of normal appearance except for the small flailed portion where a fibrous thickening was observed. The change was considered to be secondary to regurgitant flow. The histological changes seen in the aortic valve were not found in the mitral valve. In this patient there may have been histopathological degeneration in the aortic valve before the accident that made it more vulnerable to the forces generated by steering wheel compression.

References

1 Kay JH, Zubiate P, Mendez MA, Vanstrom N, Yokoyama T. Mitral valve repair for significant mitral insufficiency. *Am Heart J* 1978;**96**:253–62.

2 De Vega NG. La annuloplastia selectiva regulable y permanente. Una tècnica originale para et tratamiento de la insuficiencia tricuspide. *Rev Esp Cardiol* 1972;**25**:555–6.

3 Barber H. The effects of trauma, direct and indirect, on the heart. *Q J Med* 1944;**13**:137–67.

4 Cuadros CL, Hutchinson JE, Mogtader AH. Laceration of a mitral papillary muscle and the aortic root as a result of blunt trauma to the chest. *J Thorac Cardiovasc Surg* 1984;**88**:134–40.

5 Parmley LE, Manion WC, Mattingly TW. Nonpenetrating traumatic injury of the heart. *Circulation* 1958;**18**:371–96.

6 Kissane RW, Fidler RS, Koons RA. Electrocardiographic changes following external chest injury to dogs. *Ann Intern Med* 1937;**11**:907–35.

7 Sklar JS, Clarke D, Campbell D, Pearce B, Apperetti K, Johnson M. Traumatic ventricular septal defect and lacerated mitral leaflet. *Chest* 1982;**81**:247–9.

8 Rashid A, Chandrarata PA, Hildner FJ, Samet P, Yahr WZ, Greenberg J. Papillary muscle rupture following nonpenetrating chest trauma. Report of a case with hemodynamic and serial echocardiographic findings and successful surgical treatment. *Heart Lung* 1978;**7**:647–51.

9 Miller FA, Seward JB, Gersh BJ, Tajik AJ, Mucha P. Two-dimensional echocardiographic findings in cardiac trauma. *Am J Cardiol* 1982;**50**:1022–7.

10 Faillace RT, Greenland P, Nanda NC. Rapid expansion of a saccular aneurysm on the left coronary sinus of Valsalva: a role for early surgical repair? *Br Heart J* 1985;**54**:442–4.

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A functioning intrapericardial paraganglioma (pheochromocytoma)

YOSHIAKI SHIMOYAMA, KOZO KAWADA, HIROJI IMAMURA

From the Department of Surgery, Keio University Hospital, Tokyo, Japan

SUMMARY A patient with a functioning intrapericardial paraganglioma (pheochromocytoma) that was located at the root of the aorta overlying the right coronary artery and adherent to the right ventricular wall is reported. The tumour was successfully removed under total cardiopulmonary bypass without inducing cardiac arrest.

Since 1974 when Besterman *et al* reported an intrapericardial pheochromocytoma,[1] other cases have been reported.[2-10] In most reported cases[1-6] the tumour seemed to be related to the left atrial wall. We report a case in which the pheochromocytoma was located at the root of the aorta.

Case report

About 10 years before presentation this 49 year old woman had first noted palpitation, headache, and weakness in her feet. Appendectomy (at age 19) and two pregnancies and deliveries (at 27 and 31) had been uneventful. She had an intraoperative hypertensive crisis and a postoperative hypotensive crisis at total hysterectomy and bilateral adnexectomy at 43.

On 16 February 1980, she was admitted to the Keio University Hospital. She was of normal size and shape, and had two abdominal scars. No mass was palpable in the abdominal area. Blood pressure was 150/80 mm Hg and rose to 210/110 mm Hg within a few minutes of the intravenous injection of 10 mg of metoclopramide.[11] Urinary excretion of noradrenaline was 4782 nmol/24 h (809 μg/24 h) (normal 59–532 nmol/24 h) (10 to 90 μg/24 h) and the concentration of plasma noradrenaline was 12·05 nmol/l (2·04 ng/ml) when the patient was recumbent (normal < 2 4 nmol/l (0·40 ng/ml). We suspected that she had a pheochromocytoma.

Because the site of the tumour was not known she was treated with labetalol (400 mg per day). On 14 October 1985 she was readmitted to our hospital because of an attack of paroxysmal hypertension and palpitation. Urinary excretion of noradrenaline was 25·7 μmol/24 h (4352 μg/24 h) and the concentration of plasma noradrenaline while the patient was recumbent was 36 nmol/l (6·10 ng/ml). On 20 November 1985 whole body ^{131}I-metaiodobenzylguanidine scintigraphy revealed a lesion in the thorax (fig 1a). Computed tomography of the chest on 4 December 1985 showed an abnormal mass in the mediastinum (fig 1b). On 13 December 1985 an arteriogram obtained after injection of contrast into the left internal mammary artery showed hypervascularity of the upper part of the tumour (fig 2).

At operation on 22 January 1986 a dark red and smooth tumour was found when the pericardium was opened. The tumour arose from the root of the aorta; it overlay the right coronary artery and adhered to the right ventricular wall. It was removed under total cardiopulmonary bypass and mild hypothermia without inducing cardiac arrest. The tumour was supplied with many arteries derived from the right coronary artery. The tumour was removed together with a part of the right ventricular myocardium.

The patient's blood pressure became normal on the first postoperative day. After operation urinary excretion of noradrenaline fell to 893 nmol/24 h (151 μg/24 h) and plasma noradrenaline fell to 2 nmol/l (0·34 ng/ml). Her blood pressure did not increase after intravenous metoclopramide.[11] She was discharged on the twenty-fifth postoperative day off medication.

The tumour measured 5·0 × 4·5 × 3·5 cm. The cut area showed a homogeneous, brown mass of

Requests for reprints to Dr Yoshiaki Shimoyama, Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160, Japan.

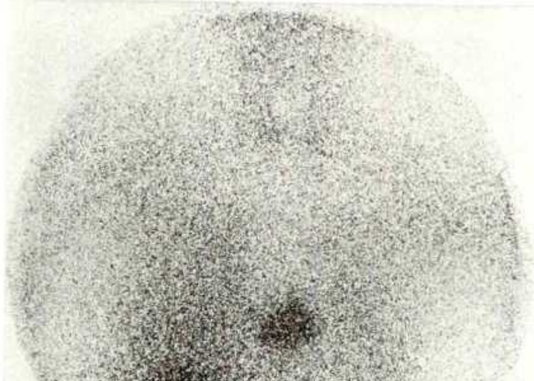

Fig 1 *(a) ^{131}I-metaiodobenzylguanidine scintiscan (anterior image of chest), three hours after a dose of 1·0 mCi, showing lesion in the thorax. (b) Computed tomographic scan of the chest showing an abnormal mass (arrow).*

nodular tissue. The tumour was surrounded by a collagenous capsule and was firmly attached to the myocardium, but there was no infiltration of the myocardium. There were many blood vessels, some of which were dilated and some which were compressed. The tumour cells were arranged in clusters of various sizes which were separated by fibrous septa. The tumour cells had egg shaped hyperchromatic nuclei of slightly varying sizes, but active mitotic figures were not seen. Many had cytoplasmic vacuoles. The tumour cells contained abundant cytoplasmic granules (fig 3). Strong staining of the granules by the Grimelius silver reaction suggested that these were secretory granules (fig 3).

Electronmicroscopy showed that the chief cells contained cytoplasmic granules with an electron-dense core (fig 3). The diameter of these secretion granules ranged from 150 nm to 200 nm. The tumour contained 3·34 mg of noradrenaline per gram but not adrenaline or dopamine. The tumour was identified as a benign functioning paraganglioma (pheochromocytoma).

Discussion

Intrapericardial paragangliomas are rare tumours. There are two types. The first are called chemodectomas; they are chromaffin negative and they originate from the parasympathetic chain and are seen in chemoreceptor tissue. According to Gopalakrishnan *et al* these tumours are non-functioning in the intrapericardial site.[12] The second group comprises the pheochromocytomas which are chromaffin positive and arise from the sympathetic nervous system. These tumours are catecholamine secreting and functioning paragangliomas. Intrapericardial pheochromocytomas usually involve the left atrial wall. Shapiro and colleagues reported six pheochromocytomas originating from the left atrium and another detected in the aortopulmonary window.[5] Besterman *et al*, Wilson *et al*, Voci *et al*, Saad *et al*, and Fisher *et al* have all reported cases in which a pheochromocytoma was attached to the left atrium.[1-4 6] Others have described pheochromocytomas arising from the interatrial septum.[7 8] David *et al* reported a case in which a pheochromocytoma involved the posterior wall of the left ventricle and coronary sinus.[9] A right atrial pheochromocytoma has also been reported.[10]

To our knowledge, a pheochromocytoma arising from the root of the aorta, overlying the right coronary artery, and adherent to the right ventricular wall has not been described before. A tumour at this site is likely to have arisen from chromaffin cells of the paraganglia in the ventral connective tissues between the descending aorta and the pulmonary trunk. This paraganglion is called the coronary paraganglion and receives its blood supply from the left coronary artery in adults.[13] Boyd has pointed out that in the fetus the coronary paraganglion receives an additional blood supply from the right coronary artery.[14] The fact that the tumour in our patient was mainly supplied from the right coronary artery suggests that this artery may supply the coronary paraganglia in adults as well. Angiography showed that the upper part of the tumour was supplied from the left internal mammary artery. Because there may be anastomoses between the coronary arteries and the internal mammary artery,[15] it is not impossible that a branch of the internal mammary artery supplied the region in which the tumour was found. We

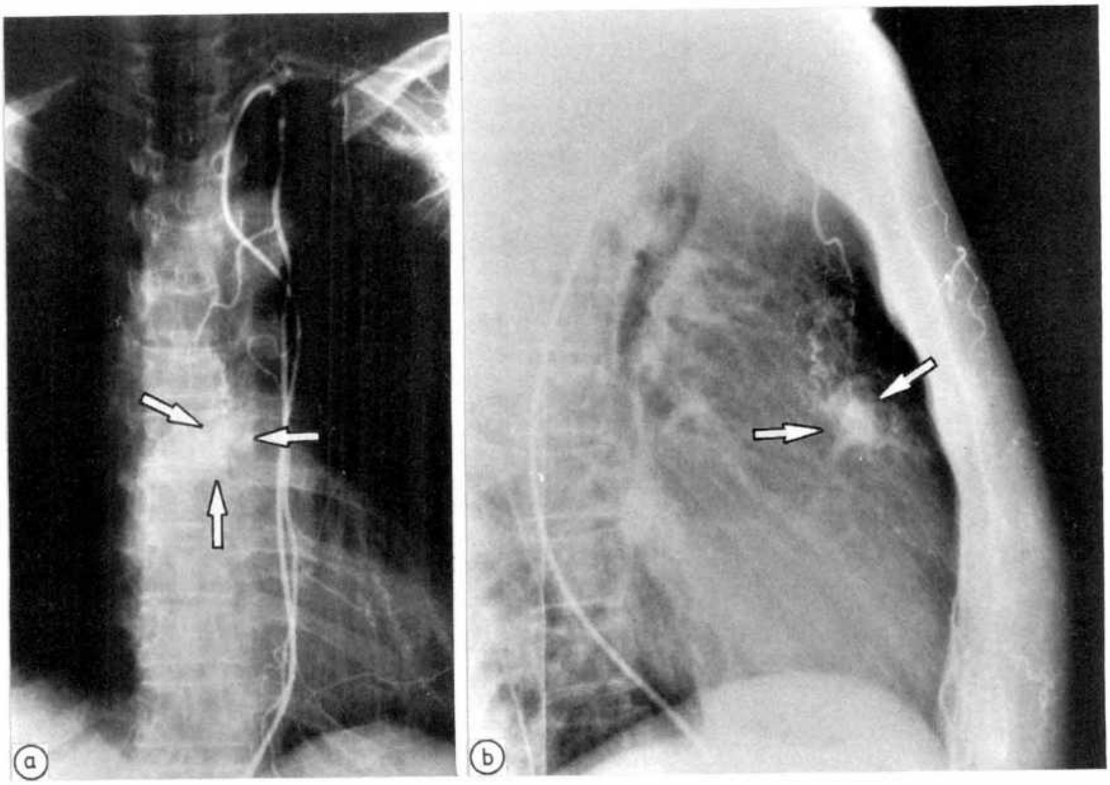

Fig 2 *Arteriograms obtained after injection of contrast into the left internal mammary artery showing hypervascularity along the upper part of the tumour (arrows).*

therefore propose that there is another blood supply to the coronary paraganglion in adults.

^{131}I-metaiodobenzylguanidine scintigraphy was most helpful in determining the site of the pheochromocytoma in this case. Computed tomography of the chest was useful in determining the anatomical connections with the intrathoracic organs. ^{131}I-metaiodobenzylguanidine is an appropriate agent for the search for extra-adrenal pheochromocytomas.

Microscopy showed that the tumour was firmly attached to the myocardium though no infiltration was noted. Removal of tumours from this site requires resection of a part of the right ventricular wall. The tumour was completely removed under cardiopulmonary bypass without any functional damage to the right coronary artery. Induction of cardiac arrest was not needed because there was no arrhythmia; thus the right ventricular wall could be reconstructed without any difficulty.

We thank Professor Tadashi Inoue and Takao Saruta for their helpful advice and criticism and Hiromichi Suzuki, Toshio Imafuku, and Hiroaki Nomori for their preoperative management of our patient. We also thank Chikao Torikata for the photomicrographs and photoelectronmicrographs.

References

1 Besterman E, Bromley LL, Peart WA. An intrapericardial phaeochromocytoma. *Br Heart J* 1974;**36**:318–20.
2 Wilson AC, Bennett RC, Niall JF, Clarebrough JK, Doyle AE, Louis WJ. An unusual case of intrathoracic pheochromocytoma. *Aust NZ J Surg* 1974;**44**:27–32.
3 Voci V, Olson H, Beilin L. A malignant primary cardiac pheochromocytoma. *Surg Rounds* 1982; **9**:88–90.
4 Saad MF, Frazier OH, Hickey RC, Samaan NA. Intrapericardial pheochromocytoma. *Am J Med* 1983; 75:371–6.

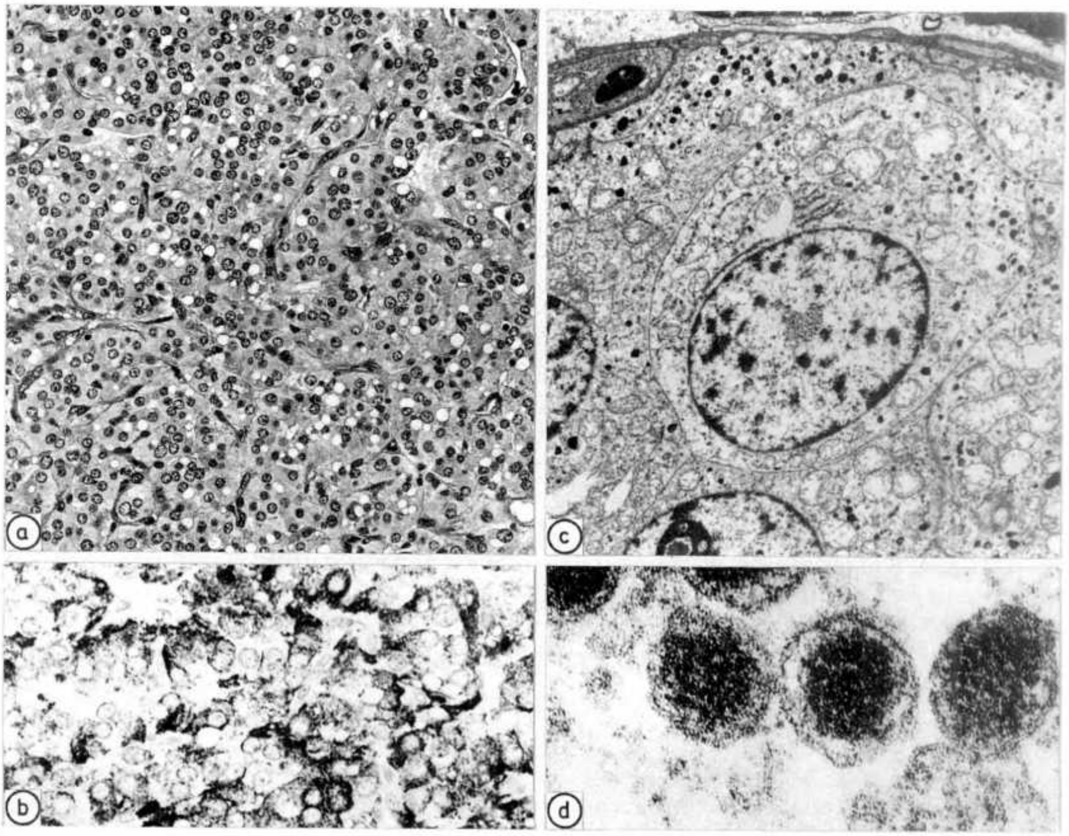

Fig 3 *(a) Photomicrograph (haematoxylin and eosin) of the tumour showing the arrangement of cells into alveoli. Tumour cells contain egg-shaped hyperchromatic nuclei and abundant cytoplasmic granules. There are vacuoles in the cytoplasm in many cells. (b) Photomicrograph (Grimelius stain) showing strong staining of cytoplasmic granules which indicates that they are secretory granules. (c) Photoelectronmicrograph of a tumour cell containing many secretion granules. (d) High power photoelectronmicrograph showing that the diameter of a granule is about 150–200 nm.*

5 Shapiro B, Sisson J, Kalff V, *et al*. The location of middle mediastinal pheochromocytomas. *J Thorac Cardiovasc Surg* 1984;**87**:814–20.

6 Fisher MR, Higgins CB, Andereck W. MR imaging of an intrapericardial pheochromocytoma. *J Comput Assist Tomogr* 1985;**9**:1103–5.

7 Hodgson SF, Sheps SG, Subramanian R, Lie JT, Carney JA. Catecholamine-secreting paraganglioma of the interatrial septum. *Am J Med* 1984;77:157–61.

8 Awoke S, Perlstein RS. Dopamine- and norepinephrine-secreting intrapericardial pheochromocytoma in a normotensive patient. *South Med J* 1985;**78**:994–8.

9 David TE, Lenkei SC, Marquez-Julio A, Goldberg JA, Meldrem DAN. Pheochromocytoma of the heart. *Ann Thorac Surg* 1986;**41**:98–100.

10 Palubinskas AJ, Roizen MF, Conte FA. Localization of functioning pheochromocytomas by venous sampling and radioenzymatic analysis. *Radiology* 1980; **136**:495–6.

11 Kawabe H, Itaya Y, Suzuki H, Kondo K, Saruta T. Metoclopramide in the diagnosis of pheochromocytoma. *Jpn Heart J* 1985;**26**:557–66.

12 Gopalakrishnan R, Ticzon AR, Cruz PA, *et al*. Cardiac paraganglioma (chemodectoma). *J Thorac Cardiovasc Surg* 1978;**76**:183–9.

13 Glenner GG, Grimley PM. Tumors of the extra-adrenal paraganglion system (including chemoreceptors). In: Firminger HI, ed. *Atlas of tumor pathology*, second series, fascicle 9. Washington DC: Armed Forces Institute of Pathology, 1974:17–33.

14 Boyd JD. The inferior aortico-pulmonary glomus. *Br Med Bull* 1961;**17**:127–31.

15 Moberg A. Anastomoses between extracardiac vessels and coronary arteries. *Acta Med Scand* 1968; **485**(suppl):5–26.

Br Heart J 1987;57:384–6

Nocardial endocarditis of an aortic valve prosthesis

GEORG ERTL,* KLAUS P SCHAAL,† KURT KOCHSIEK*

*From the *Department of Medicine, University of Wurzburg, and the †Institute for Medical Biology and Immunology, University of Bonn, Federal Republic of Germany*

SUMMARY The organism responsible for endocarditis of a prosthetic aortic valve was identified as *Nocardia asteroides*. The patient was treated with intravenous amikacin (250 mg four times a day) and intravenous imipenem (1·5 g four times a day). The valve was replaced under this new antibiotic regimen. This is the first report of survival after prosthetic valve nocardiosis.

Two cases of endocarditis of a prosthetic valve resulting from *Nocardia asteroides* infections have been reported.[1 2] Both patients died before specific treatment could be established. We report a case of nocardial endocarditis that followed aortic valve replacement.

Case report

A 61 year old man with severe calcific aortic valve disease was given a Medtronic Hall valve prosthesis in March 1984. Fever developed after operation and he was treated with the antibiotic cefadroxil because an exacerbation of chronic emphysematous bronchitis was suspected. The patient was transferred to the medical department 21 days after operation. Physical examination was normal and the prosthetic heart sounds were clear. A chest *x* ray indicated emphysema without pulmonary infiltrates; the heart was of normal size. Abdominal sonography and cholangiography showed small stones in the gall bladder and in the cystic duct. The erythrocyte sedimentation rate (56 mm per hour), the neutrophil count ($5·7 \times 10^9$/l) (with an increased proportion of unsegmented neutrophils (11%), serum iron (<25 μg/dl), and copper (240 μg/dl)) were compatible with a systemic infection. When antibiotic treatment was withdrawn the patient's oral temperature rose to 40°C. After two weeks of incubation at 37°C blood cultures showed growth of a Gram positive filamentous micro-organism. This organism was identified as biovar B of the *Nocardia asteroides* complex[3] or *Nocardia farcinica*.[4] Sputum cultures were always negative for nocardiae and urine cultures contained no micro-organisms.

TREATMENT

Intravenous treatment with amoxycillin (2 g three times a day) was started followed by a combination of mezlocillin (5 g three times a day) and tobramycin (80 mg twice a day) because blood cultures remained negative for two weeks. When *Nocardia asteroides* was identified as the aetiological agent treatment with sulphadiazine 12 g a day was started. But the dose of 24 tablets per day produced unacceptable gastrointestinal side effects. Intravenous treatment with amikacin and a combination of amoxycillin plus clavulanic acid (Augmentin) was started at dosages of 250 mg two to four times a day and 5·5 g three times a day (5 g amoxycillin + 0·5 g clavulanic acid), respectively. In vitro susceptibility tests[5] showed that the *Nocardia* strain was sensitive to amikacin at a minimal inhibitory concentration (MIC) of 2 μg/ml and moderately sensitive to amoxycillin plus clavulanic acid (MIC 8–16 μg/ml) and the thienamycin derivative, imipenem (MIC 8 μg/ml). Oral dosages of imipenem (1·5 g four times a day) and amikacin (500 mg four times a day) were chosen to maintain the bactericidal concentrations in the serum that were obtained during infusion of both drugs. This regimen reduced fever to 37–38°C and reduced the proportion of unsegmented neutrophils.

Six weeks after admission, moderate signs of cholangitis were seen and a cholecystectomy was performed in the eighth week. Cultures from the removed gall bladder, the bile, and blood were negative. Body temperature declined and remained normal for four weeks and the patient was discharged on the thirteenth postoperative day without antibiotic treatment.

The patient was readmitted to the medical department on 30 July 1984 because of recurrent septic fever. Blood cultures again produced *Nocardia asteroides (N farcinica)* which was still sus-

Requests for reprints to Dr Georg Ertl, Medizinische Klinik der Universitat, 8700 Wurzburg, Federal Republic of Germany.

ceptible to amikacin, imipenem, and co-trimoxazole in vitro. Clinical investigation, especially prosthetic valve sounds and laboratory tests including chest *x* ray, bronchoscopy, abdominal sonography, and bone marrow histology did not indicate any systemic malignant disease. On the second day of amikacin treatment (500 mg four times a day) and imipenem (1 g four times a day) fever levelled off and remained at 36·5–37·5°C. The patient was transferred to the department of surgery. At operation an intact aortic valve prosthesis was found but there was an aneurysm of the non-coronary sinus of Valsalva. Cultures from the removed valve produced *Nocardia asteroides (N farcinica)*. The sinus of Valsalva and the base for the valve were locally disinfected and a Medtronic Hall aortic valve prosthesis was implanted. Postoperative recovery was good. Amikacin had to be withdrawn because of rapid deterioration of hearing. Treatment with imipenem (1 g four times a day) was continued for three weeks after operation. Then the patient was treated with oral trimethoprim and sulphamethoxazole (160 and 800 mg twice a day respectively). Before discharge transmission computed tomography and scintigraphy with indium-111 labelled leucocytes did not detect any cranial abscesses. The patient remains well without any laboratory evidence of infectious disease.

Discussion

Nocardiosis is a rare disease with an unfavourable prognosis which occurs predominantly in severely compromised patients with systemic malignant disease or in those on immunosuppressive treatment.[6] So far two cases of nocardiosis of prosthetic valves have been reported.[1 2] Vlachakis and associates reported the death of a 34 year old women four months after mitral valve replacement.[2] Falk and coworkers reported the death of a 64 year old woman from nocardial endocarditis six months after replacement of an aortic valve.[1] Both patients had multiple abscesses and in the absence of other sites of entry the lungs were the most likely portal for systemic nocardiosis.[6] In our patient body temperature declined to normal immediately after cholecystectomy; however, an infectious agent was not cultured from the resected gall bladder and cholangitis or cholecystitis have not been reported as primary manifestations of nocardiosis. The possibility of false negative cultures must be considered; however, the mode of infection remains unclear. Possibilities include intraoperative infection and activation by the operation of an infection that was acquired preoperatively.[7]

This is the first report of the survival of a patient with nocardial endocarditis after valve replacement. In our opinion the favourable outcome in this case depended on the following factors: (*a*) the causative agent (*Nocardia asteroides*, biovar B = *N farcinica*) was identified early; (*b*) abscesses did not occur in vital organs; (*c*) an antibiotic regimen that was effective in vivo was found; and the patient could be brought to reoperation.

Nocardiosis was diagnosed in our patient from a blood sample obtained on the twenty-sixth postoperative day. Because we found that only screening for *Nocardia* gave positive results, we wonder whether the high numbers of "unknown" agents in prosthetic valve endocarditis[8] may be partly accounted for by nocardiae. Early diagnosis is essential because nocardiosis tends to spread and produce disseminated, especially cerebral, abscesses.[6 7] Prevention of these abscesses was probably the major effect of the antibiotic treatment that we used. We used a regimen of amikacin and amoxycillin plus clavulanic acid because experimental[5] and clinical[9] results with these agents have been reported to be better than standard sulphadiazine treatment. The *Nocardia* strain in the present case was sensitive to amikacin but only moderately sensitive to amoxycillin plus clavulanic acid (Augmentin) and fever was not suppressed by this combination. Augmentin was, therefore, replaced with the thienamycin derivative imipenem which has also been reported to be effective in some isolates of *Nocardia asteroides*.[10 11] Imipenem appeared to be as effective or slightly more effective against the patient's *Nocardia* strain than amoxycillin plus clavulanic acid. Very high doses were required to achieve bactericidal plasma concentrations and after the replacement of the valve prosthesis the side effects of amikacin (deterioration of hearing) limited the use of this drug. Antibiotic treatment could not be expected to effect a cure in the presence of an infected valve prosthesis. The positive cultures obtained from the removed aortic valve prosthesis and the rapid recovery of the patient after replacement of the valve confirmed the diagnosis of nocardial endocarditis. The contribution of the aneurysm of the sinus of Valsalva in this case is not known. Cultures obtained from this aneurysm were negative and we do not know whether it was a consequence or a cause of the endocarditis.

We thank Professor Gerhard Schroeter, Institute of Hygiene and Professor Olaf Elert, Department of Thoracic and Cardiovascular Surgery, University of Würzburg for their cooperation.

References

1 Falk RH, Dimock FR, Sharkey J. Prosthetic valve endocarditis resulting from *Nocardia asteroides*. *Br Heart J* 1979;**41**:125–7.

2 Vlachakis ND, Gazes PC, Hairston P. Nocardial endocarditis following mitral valve replacement. *Chest* 1973;**63**:276–8.

3 Schaal KP. Laboratory diagnosis of actinomycete diseases. In: Goodfellow M, Mordarski M, Williams ST, eds *The biology of the actinomycetes*. London, Orlando, New York: Academic Press, 1984:7–164.

4 Goodfellow M, Cross T. Classification. In: Goodfellow M, Mordarski M, Williams ST, eds. *The biology of the actinomycetes*. London, Orlando, New York: Academic Press, 1984:7–164.

5 Schaal KP, Schutt-Gerowitt H, Goldmann H. *In vitro* and *in vivo* studies on the efficacy of various antimicrobial agents in the treatment of human nocardiosis. In: Szabo G, Biro S, Goodfellow M, eds. *Biological, biochemical and biomedical aspects of actinomycetes*. Part B. Budapest. Akadémia Kiado, 1986:619–33.

6 Palmer DL, Harvey RL, Wheeler JK. Diagnostic and therapeutic considerations in *Nocardia asteroides* infection. *Medicine (Baltimore)* 1974;**53**:391–401.

7 Schaal KP, Beaman BL. Clinical significance of actinomycetes. In: Goodfellow M, Mordarski M, Williams ST, eds. *The biology of the actinomycetes*. London, Orlando, New York: Academic Press, 1984:7–164.

8 Ivert TSA, Dismukes WE, Cobbs CG, Blackstone EH, Kirklin JW, Bergdahl LAL. Prosthetic valve endocarditis. *Circulation* 1984;**69**.223–32.

9 Stasiecki P, Diehl M, Vlaho M, Krueger GRF, Schaal KP. Neue erfolgreiche Therapie bei systemischen Infektionen mit *Nocardia asteroides*. *Dtsch Med Wochenschr* 1985;**110**:1733–7.

10 Cynamon MH, Palmer GS. *In vitro* susceptibility of *Nocardia asteroides* to N formidoyl thienamycin and several cephalosporins. *Antimicrob Agents Chemother* 1981;**20**:841–2.

11 Gutmann L, Goldstein FW, Kitzis MD, Hautefort B, Darmon C, Acar JF. Susceptibility of *Nocardia asteroides* to 46 antibiotics including 22 β-lactams. *Antimicrob Agents Chemother* 1983;**23**:248–51.

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Congenital fistula between the aorta and left atrium

PETROS NIHOYANNOPOULOS, RALPH SAPSFORD, CELIA M OAKLEY

From the Departments of Medicine (Clinical Cardiology) and Surgery (Cardiovascular), Royal Postgraduate Medical School, Hammersmith Hospital, London

SUMMARY A child in whom abnormal vessels connected the descending thoracic aorta and the left atrium is described. This is a previously unreported congenital malformation. Clinically this condition differs from the more common aorto-cardiac fistulas in that the continuous murmur was better heard posteriorly as well as in the right parasternal area. Ligation of the aberrant vessels abolished the murmur.

Aorto-cardiac fistulas are well known. Aneurysms of the sinuses of Valsalva, usually of the right sinus, may rupture into the right ventricle, right atrium, or rarely the left atrium.[1 2] The communications are rarely congenital. They rupture either spontaneously or as a result of infection, trauma, or operation involving the aorta or aortic valve.[3–5]

An aorto-left ventricular tunnel is a congenital anomaly in which a defect in the aortic wall provides a tunnel opening on to the left ventricle via the septum bypassing the aortic valve.[6] Coronary cameral fistulas are usually congenital and caused by an abnormal connection between a main or branch coronary artery and one of the cardiac chambers.[7]

We report a patient in whom there were congenital fistulas between the abnormal branches of the descending thoracic aorta and the left atrium. We found no published reports of similar cases.

Case report

A four year old Iranian boy was admitted for investigation of a cardiac murmur. He was born after a normal pregnancy and was healthy until he had a "gland" infection at the age of two. Then a heart murmur was discovered.

On examination he was of normal size and build for his age, apart from a precordial bulge caused by an enlarged heart. He was intelligent and cooperative. He was acyanotic with no clinical signs of heart failure. The arterial pulses were regular and symmetrical; however, they were of high volume and ill-sustained. Blood pressure was 90/40 mm Hg. The venous pressure was normal. The left ventricle was greatly enlarged and showed a hyperkinetic impulse. A very loud continuous murmur was heard on auscultation. This was best heard posteriorly to the right of the spine at the level of T5 and T6, but it was also heard widely over the back and much more softly anteriorly. There was an apical third heart sound. The electrocardiogram showed sinus rhythm with voltage criteria typical of left ventricular enlargement. Chest x ray showed considerable cardiomegaly and a large aortic knob. The main pulmonary artery was not enlarged and there was no evidence of a left to right shunt.

Cross sectional echocardiography showed situs solitus with normal intracardiac relations. There were no valvar abnormalities. The left ventricle was enlarged and contracting vigorously. The left atrium was also dilated, whereas the right heart chambers were normal. The ventricular septum was intact. There was no evidence of coarctation. The ascending aorta and the horizontal portion of the arch were enlarged and excessively pulsatile as far as the isthmus. At the isthmus a large vessel appeared to emerge from the descending aorta. This was taken to be a ductus arteriosus even though its continuity with the pulmonary artery was not visualised on the echocardiogram. Because the clinical findings were incompatible with a ductus arteriosus, cardiac catheterisation and angiography were performed. There was no pressure gradient across the valves. An aortogram showed a competent aortic valve and no ductus arteriosus. After the arch of the aorta became opacified the left atrium filled promptly through a large channel which appeared to lie posteriorly and parallel to the descending aorta (figs 1 and 2). A

Requests for reprints to Dr Petros Nihoyannopoulos, Department of Medicine (Clinical Cardiology), Hammersmith Hospital, Ducane Road, London W12 0HS.

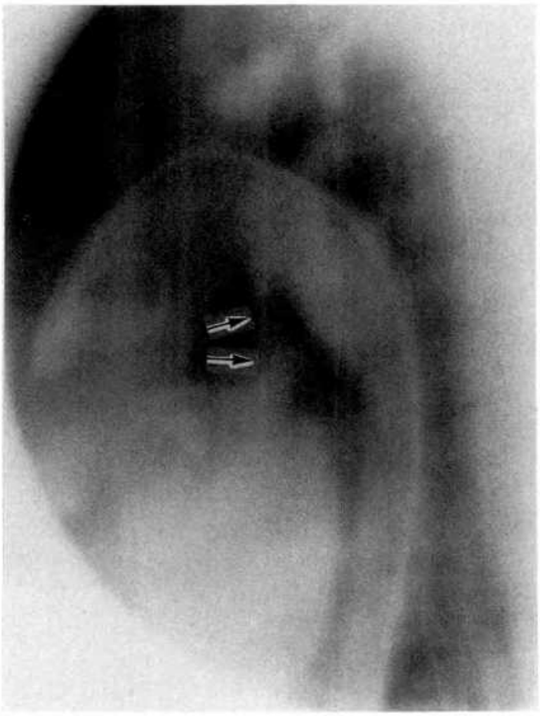

Fig 1 *Contrast aortogram in the left anterior oblique projection showing the abnormal vessel connecting the descending thoracic aorta with the left atrium (arrows). Note also the diminishing calibre of the descending thoracic aorta.*

fistula between the aorta and left atrium was diagnosed. Because neither the angiogram nor the echocardiogram had indicated the precise connections of this fistula the patient was examined by computed tomography. This showed an anomalous vessel adjacent and to the right of the descending thoracic aorta which appeared in images immediately below the arch of the aorta at a point where the calibre of the aorta abruptly diminished. This structure filled with the contrast to the same degree as the aorta and was of a similar size (fig 3).

Laboratory investigations were normal apart from an iron deficiency anaemia (haemoglobin 9·1 g/dl). The tuberculin test was negative.

Operation was performed through a left thoracotomy incision. The aortic arch was large and at the base of a large left subclavian artery there was an abnormal vessel of the same diameter as the left subclavian artery. After about 1·5 cm this anomalous vessel petered out into a fibrous chord and disappeared into the mediastinum in the region of the oesophagus. About 2 cm below the origin of the left subclavian artery the descending thoracic aorta rapidly tapered down to about half the size of the arch. There was a very strong continuous thrill in this area. After the third part of the arch and the descending thoracic aorta had been fully dissected and mobilised, it was possible to see a very large vessel passing directly to the right from the descending thoracic aorta just where it started to narrow and there was a further vessel about half its diameter immediately above it. Because the thrill only disappeared after trial occlusion of both aberrant vessels, they were evidently in direct communication. Both vessels were doubly ligated and this abolished the thrill. The patient's postoperative course was uneventful. Figure 2 is a compositive diagrammatic representation of the angiographic, computed tomographic, and operative findings.

Discussion

Aorto-cardiac communications are not uncommon in children and neonates. The large gradient between the high pressure aorta and low pressure cardiac chamber causes a high flow for which the heart must compensate to maintain adequate perfusion.[8] Most congenital aorto-cardiac fistulas communicate between one of the coronary sinuses, usually the right, and the right ventricle, right atrium, and much more rarely the left ventricle. These fistulas are often associated with other congenital heart lesions.[1] Jaen *et al* described a patient with a

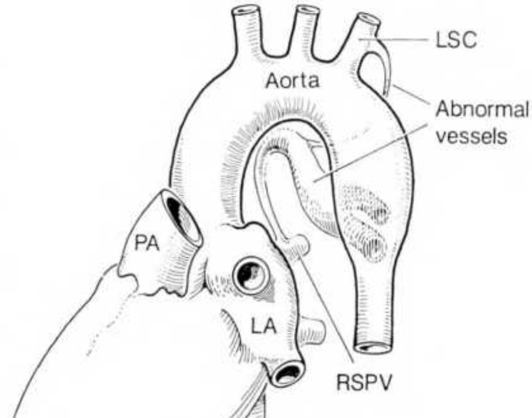

Fig 2 *Diagrammatic representation of the aortic arch viewed from the left lateral projection with the pulmonary artery removed for clarity (see text). IVC, inferior vena cava; LA, left atrium; LSC, left subclavian artery; PA, pulmonary artery; RSPV, right superior pulmonary vein.*

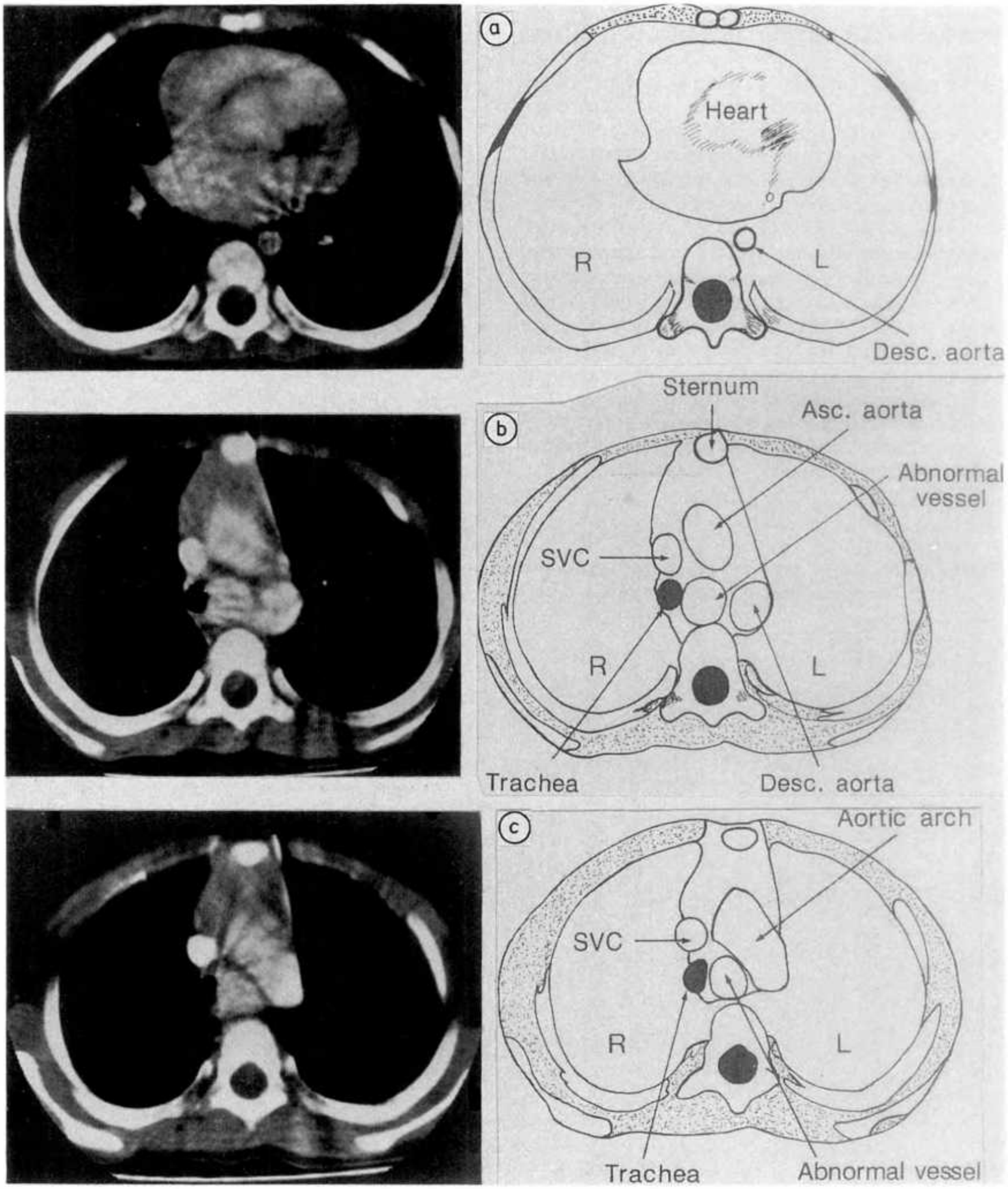

Fig 3 *Computed tomographic scan at the level of the heart (a) and great vessels (b, c). After contrast injection (b, c) the abnormal vessel became opacified simultaneously with the ascending and descending aorta (b) and the transverse portion of the arch (c). The calibre of the descending thoracic aorta at the level of the heart (a) is half the size of the arch (c).*

communication between the ascending aorta, 3 mm above the origin of the left coronary artery, and the left atrium, which led to the formation of four large aneurysmal sacs.[9]

After birth, acquired communications occur either as varicose aneurysms or as direct arteriovenous anastomoses caused by trauma, operation, or infection.[8] Apart from the unspecific history of a gland infection and the site of communication in our patient there is nothing to suggest that this communication may have been developed after birth. The smoothly communicating vessels with the presence of a second similar but much smaller vessel, the lack of fibrous tissue or adhesions, and the young age of our patient all indicate that these were anomalous branches of the aorta communicating directly with the left atrium. These vessels arose where one would expect the right sided intercostal vessels to arise from the descending thoracic aorta. The direct communication with the left atrium, however, is hard to explain embryologically.

We thank Dr Louis Kreel for providing fig 3 and for his expert interpretation of the computed tomographic scan.

References

1 Nowicki ER, Aberdeen E, Friedmann S, Rashkind WJ. Congenital left aortic sinus-left ventricle fistula and review of aortocardiac fistulas. *Ann Thorac Surg* 1977;23:378–88.

2 DeBakey ME, Diethrich EB, Liddicoat JE, *et al.* Abnormalities of the sinuses of Valsalva. *J Thorac Cardiovasc Surg* 1967;54:312–32

3 DeSa'Neto A, Padnick MB, Desser KB, Steinhoff NG. Right sinus of Valsalva—right atrial fistula secondary to non-penetrating chest trauma. *Circulation* 1979;60.205–9.

4 Datta PK, Vickery CH Arteriovenous fistula from rupture of major arterial aneurysms. *J R Coll Surg Edinb* 1979;24:165–6.

5 Crean PA, Reid DS, Buchanan J. Aorto-atrial fistula in rheumatoid arthritis *Ann Rheum Dis* 1983;42:203–5.

6 Ribeiro P, Bun-Tan LB, Oakley CM. Management of aortic left ventricular tunnel. *Br Heart J* 1985;54:333–6.

7 Urrutia-S CO, Falaschi G, Ott DA, Cooley DA. Surgical management of 56 patients with congenital coronary artery fistulas. *Ann Thorac Surg* 1983; 35:300–7.

8 Hudson REB. *Cardiovascular pathology*. London: Edward Arnold, 1970;3:333–8.

9 Jaen R, Fermin H, Verlarde H, Lairet A, Silva G. Aorto-left atrial fistula. *J Cardiovasc Surg (Torino)* 1986;27:355–8.

Br Heart J 1987;57:391–2

Obituary

Kenneth Shirley Smith

Kenneth Shirley Smith died on 29 January 1987. He was born in 1900 and pursued a long and distinguished career in cardiology. He was a senior scholar at the Middlesex Hospital Medical School, was awarded a BSc with first class honours in 1923, and qualified MB BS in 1927. He proceeded to MRCP in 1927 and an MD in 1929. He was elected a fellow of the Royal College of Physicians in 1933. After house appointments he became medical registrar at the Middlesex Hospital and then resident medical officer at the National Heart Hospital in 1927.

Subsequently he was appointed consultant physician to Charing Cross Hospital, the London Chest Hospital, and the Samaritan Hospital for Women. He served in the Royal Army Medical Corps during the Second World War in the First Army in North Africa and later with the Central Mediterranean Force in Italy, Greece, and Austria, retiring with the rank of Colonel. He was Gold Staff Officer at the coronation of King George VI.

After the war, Shirley Smith steadily built up his reputation in cardiology. His work (with Max Zoob) on the use of pressor agents in the treatment of shock in myocardial infarction provoked interest and marked a new approach in the use of sympathomimetic drugs in cardiac crises. His interests in cardiology centred mainly on ischaemic heart disease and he published papers on electrocardiography in minor coronary thromboses and on various forms of angina.

Shirley Smith preceded, because of his age, the introduction and explosive onslaught of catheterisation and all that it brought with it. Nevertheless, he continued to maintain a high degree of expertise and a lively interest in all forms of cardiovascular disease. His organising ability was recognised by his appointment as secretary of the First European Congress of Cardiology which was held in London in 1952 under the presidency of the late Sir John Parkinson. The success of this congress, which was a pioneering event, was generally regarded as being due largely to the efficiency and application of Shirley Smith.

But Shirley Smith's principal fame came from his able editorship of the *British Heart Journal*. Starting as associate editor, he provided a perfect alliance with the editor, the late Dr Maurice Campbell, with whom he developed a deep and abiding friendship and whom he served with great loyalty. Together they forged a journal of high merit which gained and still holds an outstanding international reputation. Eventually he succeeded to the editorship. He was an excellent editor: calm, efficient, and hardworking. He held firm views about how the journal should be run and though his attitudes may have occasionally appeared somewhat rigid, his rules of procedure and high standards of scientific merit, writing, composition, and management provided a firm base for the journal at a time when the advancing tide of cardiology was sweeping all before it. His insistence on a high standard of English made him scornful of pointless prolixity and high sounding phrases of little literary merit and dubious value.

When the time came for him to retire on the grounds of age from the National Health Service he spared no pains to see that every possible encouragement and practical help was given to his successor.

His career was enhanced by his election as president of the British Cardiac Society in 1964.

Kenneth Shirley Smith was an extremely courteous person of gentle mien with a quiet and quizzical sense of humour. His sympathetic and unassuming manner sometimes misled acquaintances into thinking him dull or colourless but this was not so; within the gentle carapace of courtesy lay a strand of steel. He could be determined and forceful. His strength of character lay in his ability to act decisively and firmly without losing his friendly diplomatic approach.

In the later part of his active career he bore the fatal illness of his wife with great fortitude and courage.

Shirley Smith's contributions to cardiology were numerous, and the more notable because they were achieved in low key without fuss or excitement.

J F Goodwin

On the occasion of the retirement in 1972 of Kenneth Shirley Smith as editor of the *British Heart Journal* Walter Somerville, his successor, wrote:

. . . With the production of the December issue of the Journal, Kenneth Shirley Smith vacated the editorial chair which he had occupied since 1959. He succeeded Maurice Campbell who had been Editor since the birth of the Journal in 1938. By the time Shirley Smith assumed office he was thoroughly familiar with the distinctive *genre* of the Journal which had been fashioned by Campbell and Evan Bedford who had shared editorial responsibilities for the first ten years. Bedford retired in 1948 and Campbell was left in sole charge. One of his first actions was to appoint Shirley Smith as Associate Editor. The choice was natural and successful. Shirley Smith was of scholarly inclination, and for the next decade collaborated happily with Campbell's demanding editorial requirements. He expressed his admiration and gratitude for Campbell's influence in an editorial tribute in the Journal, regarding him as the Journal's progenitor and formative influence.

In the 14 years of his reign, Shirley Smith continued the evolutionary process, imposing his strong and sensitive policies on the Journal's personality. He was firm in his rejection of ambiguity in expression and inaccuracy, in uncovering false claims to originality, in rating papers according to their scientific importance, and in maintaining an unimpeachable ethical standard. His artistic sensitivity was reflected in his concern for basic standards of presentation. He was never disturbed by the lack of a high literary style; a writer's way of expressing himself was his own business, but he was always required to make his meaning clear and with as few words as possible consistent with this objective. Otherwise Shirley Smith's only intrusion into an author's choice of words was his implacable distaste of certain prevalent clichés. . . .

The Journal flourished under Shirley Smith's guidance: in the course of 14 years the number of pages in each volume more than doubled, the Journal advanced to monthly publication (initially quarterly), and the circulation increased by more than 75 per cent. . . .

Techniques of communication will change in time and we hope to play our proper part in evolving them. Meanwhile we . . . are grateful for the prosperous order in which he left his charge.

Br Heart J 1987;57:393–6

Correspondence

Detection of coronary artery disease by thallium scintigraphy in patients with valvar heart disease

Sir,
The results reported by Huikuri *et al* (1986;56:146–51) who used thallium scintigraphy to detect coronary artery disease in patients with valvar disease do not accord with what we found in similar patients. We used thallium-201 scintigraphy to study a group of 21 patients with severe aortic valve disease (nine with aortic stenosis, five with aortic regurgitation, and seven with combined aortic stenosis and regurgitation) and angiographically normal coronary arteries and a control group of 21 young individuals free from heart disease.[1] In the image obtained after stress testing 17 of the 21 patients with aortic valve disease had thallium uptake defects with partial or total redistribution. Findings were positive in only one of the controls. We concluded that so-called "ischaemic" patterns were common in patients with severe aortic valve disease and angiographically normal coronary arteries and that thallium scintigraphy had a low specificity (19%) for the diagnosis of associated coronary artery disease. In a later study we found that in patients with severe aortic regurgitation and normal coronary arteries there was a significant correlation between these defects in thallium uptake and wall motion abnormalities detected by equilibrium gated radionuclide angiography.[2]

In contrast, Huikuri *et al* found that thallium scintigraphy had a sensitivity and specificity of about 90% in a series including 15 patients with mitral valve disease and 33 patients with aortic valve disease. We think that several factors may have contributed to this discrepancy:

(*a*) In our series higher heart rates were obtained (for similar ages) during stress testing.[1] This could reflect a higher level of cardiac work, with a higher likelihood of disclosing perfusion defects (or "relative ischaemia") with a thallium scan.

(*b*) Aortic valve disease was more severe in our series[1] with presumably a greater left ventricular mass and a smaller coronary reserve. This could explain the higher rate of "false positive" findings on thallium scans. In the series reported by Huikuri *et al* the inclusion of 15 patients with mitral valve disease could also have improved their results.

(*c*) Although in both studies a semiquantitative method was used to evaluate the thallium scans, the method used by Huikuri *et al* is less subjective (interobserver agreement of 94%) but probably not less sensitive or more specific than ours.[1]

(*d*) Huikuri *et al* regarded all scans showing hypoperfusion in any area except the apex as positive whether or not there was redistribution, whereas we regarded scans showing hypoperfusion after stress as positive only when there was partial or total redistribution in any area including the apical zone. Only three patients in our series (one with aortic stenosis, one with aortic regurgitation, and one with mixed stenosis and regurgitation) had post-stress defects limited to the apical zone with partial or total redistribution. If these three cases are excluded, however, as suggested by Pfisterer *et al*,[3] the specificity would be increased only from 19% to 33%—thus this cannot be the only reason for the different specificity values.

These factors may explain the different results obtained in both studies. The discrepancy shows that one should be cautious about claiming or denying that the thallium scan is useful for the detection of coronary disease associated with aortic valve disease. It also shows that results from a laboratory may not be comparable, particularly if different methods and interpretation criteria are used. We therefore agree with Huikuri *et al* that it is premature to state that thallium scintigraphy can replace coronary arteriography in the diagnosis of coronary artery disease in patients with valvar heart disease.

J Candell-Riera,
Servicio de Cardiología,

J Castell-Conesa,
D Ortega-Alcalde,
Servicio de Medicina Nuclear,
Ciudad Sanitaria "Vall d'Hebron",
Barcelona,
Spain.

References

1 Candell J, Ortega D, Castell J, *et al*. Gammagrafía miocárdica de esfuerzo y redistribución con talio-201 en pacientes con valvulopatía aórtica severa y coronarias

angiográficamente sanas. *Rev Esp Cardiol* 1985; **38**:332–7.
2 Castell-Conesa J, Candell-Riera J, Rius Daví A, Ortega-Alcalde D. Estudio isotópico de las alteraciones de la perfusión y contractilidad segmentaria de pacientes con valvulopatía aórtica severa y coronarias sanas [Abstract]. *Rev Esp Med Nucl* 1986;5 (suppl I):29.
3 Pfisterer M, Muller-Brand J, Brundler H, Cueni T. Prevalence and significance of reversible radionuclide ischemic perfusion defects in symptomatic aortic valve disease patients with or without concomitant coronary disease. *Am Heart J* 1982;**103**:92–6.

This letter was shown to Dr Huikuri, who replies as follows:

Sir,
We are grateful to Dr Candell-Riera and his colleagues for commenting on their experience of thallium imaging in aortic valve disease. We are somewhat surprised by their reports of low specificity.

We do not know the details of how the images were assessed in their study. It is well known that the interpretation of thallium images is subjective and it is often difficult to define abnormal thallium perfusion. Misinterpretation of irregular thallium uptake in the apical region, which was commonly seen in our study (especially in severe aortic regurgitation) and has also been described by Pfisterer *et al*,[1] is a possible source of false positives. These defects are not strictly limited to the apex, but extend partly to the inferior region. These inferoapical defects should not be regarded as representing a coronary artery disease. The peak heart rate achieved during exercise was higher in patients studied by Candell-Riera *et al*. It is possible that subendocardial ischaemia occurring during maximal exercise in critical aortic valve disease can reduce the thallium uptake of the myocardial cells and result in thallium defects despite normal coronary arteries. It has been our policy not to continue exercise until severe symptoms develop because of the possible hazards of maximal exercise testing in patients with severe aortic stenosis. This factor may explain the lower number of false positive scans in our study.

We have continued our thallium studies in patients with aortic stenosis by using dipyridamole infusion as a stress test.[2] In this pilot study we found thallium imaging to be 86% sensitive and 87% specific in detecting angiographically significant coronary artery disease. Because of these results we now prefer dipyridamole stress testing to dynamic exercise testing in patients with critical aortic stenosis. These patients often have a poor exercise tolerance which limits the usefulness of exercise testing in conjunction with thallium imaging. Coronary vasodilation with dipyridamole does not result in myocardial ischaemia in a hypertrophied left ventricle without coronary artery disease and may also improve the specificity. We certainly agree with Candell-Riera *et al* that none of the non-invasive methods can yet replace coronary angiography in patients with valvar disease and suspected concomitant coronary artery disease. More studies are needed.

Heikki V Huikuri,
Division of Cardiology,
Department of Medicine,
Oulu University Central Hospital,
Oulu,
Finland.

References

1 Pfisterer M, Muller-Braud J, Brundler H, Cueni T. Prevalence and significance of reversible radionuclide ischemic perfusion defects in symptomatic aortic valve disease patients with and without concomitant coronary disease. *Am Heart* J 1982; **103**:92–6.
2 Huikuri HV, Korhonen UR, Ikäheimo MJ, Heikkilä J, Takkunen JT. Detection of coronary artery disease by thallium imaging using a combined intravenous dipyridamole and handgrip exercise test in aortic stenosis. *Am J Cardiol* (in press).

The cause of rheumatic heart disease

Sir,
Dr William L Proudfit's recent review entitled "John Hunter: on heart disease" is a most interesting and valuable contribution. In it he mentions the question of whether Edward Jenner or Dr David Pitcairn should rightfully be credited with having initially associated valvar heart disease with precedent rheumatic fever. He suggests that Pitcairn's claim rests upon a footnote in the second edition of Dr Matthew Baillie's textbook published in 1797,[1] whereas Jenner was known to have spoken on the subject to the Gloucestershire Medical Society in 1789.[2]

There is, however, stronger evidence than this for Pitcairn's claim. On 3 April 1810 William Charles Wells read a paper entitled "On rheumatism of the heart" to the Society for the Improvement of medical and chirurgical Knowledge.[3] Wells was an observer of irrefutable precision and independence and the secretary to that quite remarkable little society. Hunter and Baillie were also both members and regular contributors. Wells knew of Jenner because Hunter had previously read to the society an interesting letter which Hunter had received from Jenner.[4]

In the introduction to his paper in 1810 Wells detailed the development of knowledge about rheumatic heart disease. There seems little reason to challenge his account. He pointed out that Morgagni and a Dr Ferriar of Manchester had both previously reported the concurrence of rheumatism and organic disease of the heart, but had considered that the association of the two diseases was merely accidental. Then "Dr David Pitcairn, about the year 1788, began to remark that persons subject to rheumatism were attacked more frequently than others with symptoms of an organic disease of the heart. Subsequent experience having confirmed the truth of this observation he concluded that these two diseases often depend on a common cause, and in such instances therefore called the disease rheumatism of the heart. He communicated what he had observed to several of his friends and to his pupils at St Bartholomew's Hospital, to which he was then physician; but no notice, I believe, was taken of his remark in any book before it appeared in the second edition of Dr Baillie's Morbid Anatomy, which was published in 1797."

Wells pointed out that a Dr Odier of Geneva had subsequently mentioned the association without attribution in a book entitled *Manuel de Médicine Pratique,* published in 1803, as had Mr David Dundas, a surgeon, in a paper published in the *Transactions of the Medical and Surgical Society of London.* Since Pitcairn had indicated that he had no desire himself to write up his cases, Wells had hoped to include the details of them with those of some cases of his own, however, "I neglected to obtain this while the opportunity existed, and I now lament my indiscretion." As a result the series of 14 cases which Wells presented in 1810 and published in 1812 were all his own. The detail of his descriptions was such that there can now be no doubt that he was dealing with what has subsequently been called rheumatic heart disease. Wells must surely, therefore, continue to be regarded as the man who wrote the original definitive description, although, as he himself was most careful to point out, credit for the conceptual advance belonged entirely to Pitcairn.

C R P George,
Concord Hospital Renal Unit,
Concord 2139,
New South Wales,
Australia.

References

1 Baillie M. *The morbid anatomy of some of the most important parts of the human body.* 2nd ed. London: J Johnson, G Nicol, 1797.
2 Regulations and transactions of the Gloucestershire Medical Society, 1789. London: Library of the Royal College of Physicians.
3 Wells WC. On rheumatism of the heart. *Transactions of a Society for the Improvement of medical and chirurgical Knowledge* 1812;**3**:373–424.
4 Jenner [E]. A process for preparing pure emetic tartar by recrystallization. In a letter to John Hunter, Esq. Read June 4, 1784. *Transactions of a Society for the Improvement of medical and chirurgical Knowledge* 1793;**1**:30–1.

This letter was shown to Dr Proudfit, who replies as follows:

Sir,
Credit for priority in science is usually based on the date of original publication or documented presentation at a meeting, although numerous abuses of this rule could be cited. I believe that this view is relevant to the association of rheumatic fever and valvar disease. No claim was made that Jenner was the first to make this association. Many books on "acute rheumatism" were published in the last third of the eighteenth century, especially MD theses in Edinburgh, and as I have not read these it is quite possible that the association was made before 1788.

Doctor David Pitcairn, a distinguished and beloved physician in London, was neither a medical writer nor a morbid anatomist. Credit for his relating rheumatism to heart disease rests with his friends Baillie and Wells. In the absence of knowledge of his definitions of "rheumatism" and cardiac abnormalities (before the days of auscultation), it is difficult to be certain what correlation he was making. In July 1789 Jenner described a young woman with a history of "acute rheumatism" and he found heart disease at postmortem examination.[1] Daniel Ludlow Jr reported a similar case to the same society a year later, also with necropsy findings. Jenner did not forget his aetiological hypothesis and in January 1805 he wrote to Caleb H Parry requesting return of his manuscript because a neighbour had died of heart disease "... which followed two or three severe attacks of acute rheumatism."[2]

This does not mean that Pitcairn had not arrived at a similar conclusion independently, but such a claim has not been documented. Fortunately, the fame of neither Jenner nor Pitcairn rests on conflicting claims. As in the case of many scientific discoveries, the observations may have been simultaneous and completely independent, and possibly not the first reported.

William L Proudfit,
The Cleveland Clinic Foundation,
9500 Euclid Avenue,
Cleveland,
Ohio 44106,
USA.

References

1 Regulations and transactions of the Gloucestershire Medical Society. London: Royal College of Physicians.
2 Jenner E. Letter to Caleb H Parry, 1805. The Alan Mason Chesney Medical Archives, The Johns Hopkins Medical Institutions, Baltimore.

Notices

British Cardiac Society

The Annual General Meeting for 1987 will take place in Dundee on 8 and 9 April 1987, and the closing date for receipt of abstracts was 6 January 1987.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

Blood vessel imaging

A residential course/workshop on Blood Vessel Imaging Using Ultrasound Techniques will be held at the Dolphin Hotel, Southampton on 11 to 13 May 1987. Details from: Mr K N Humphries, Blood Vessel Imaging Course, 5 Mossleigh Avenue, Rownhams, Southampton SO1 8FU.

Correction

Echocardiographic measurement of the normal adult right ventricle *R Foale, P Nihoyannopoulos, W McKenna, A Kleinebenne, A Nadazdin, E Rowland, G Smith*—The authors apologise for errors in their tables in this article published in the July issue (volume 56: pages 33–44). In tables 2, 3, 4, 5, and 6 1 SD should be shown; and in table 5 the value of 1 SD for absolute values (cm) in rows T8 and T10 is 0.1.

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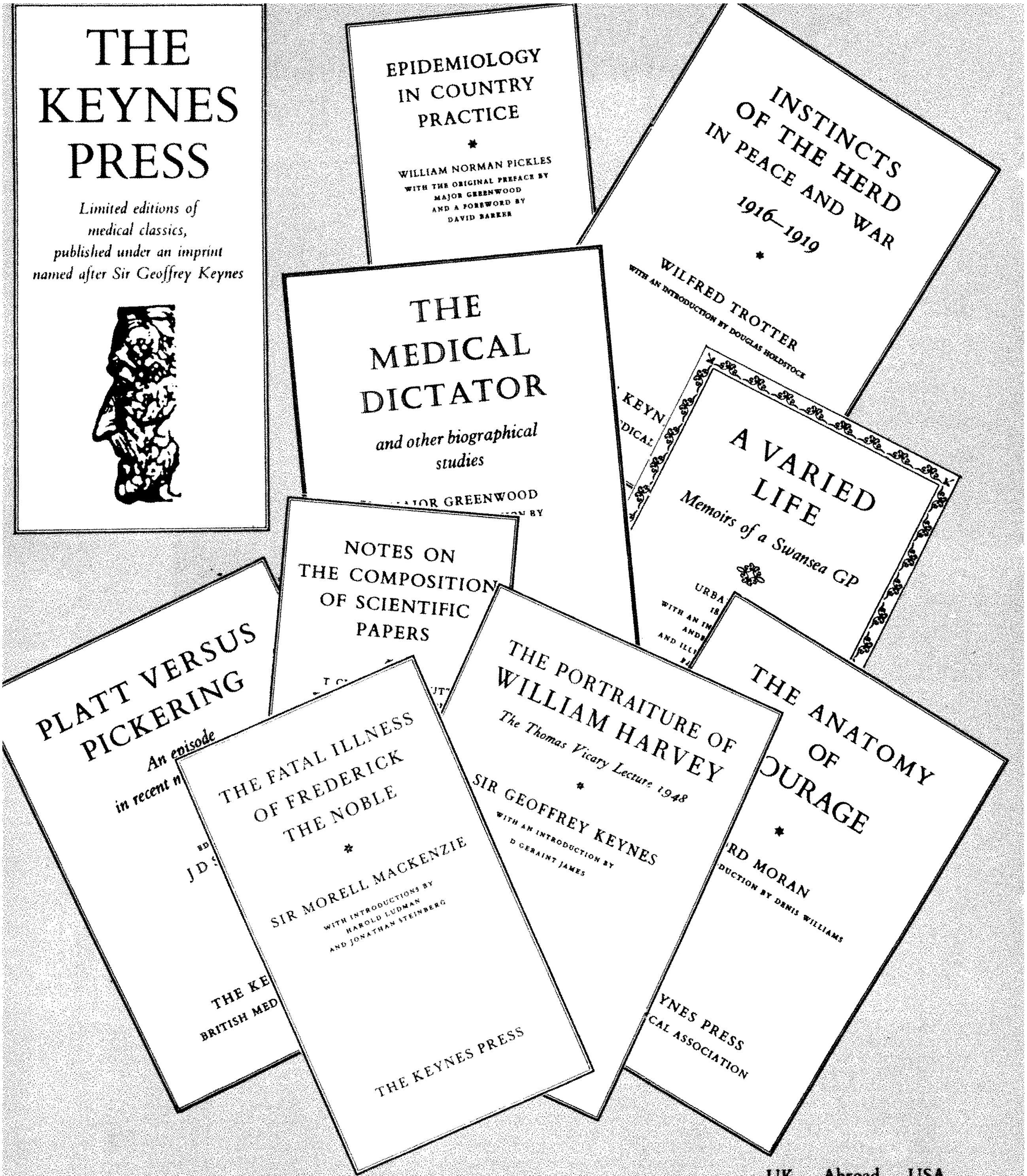

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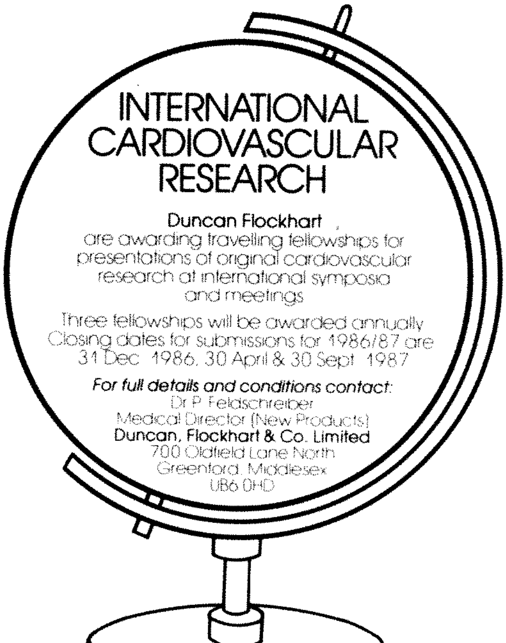

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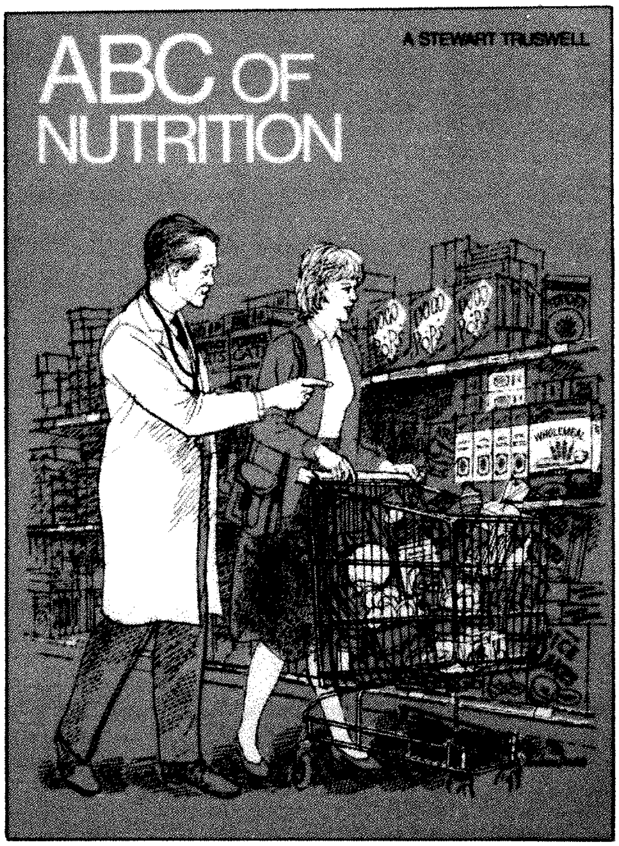

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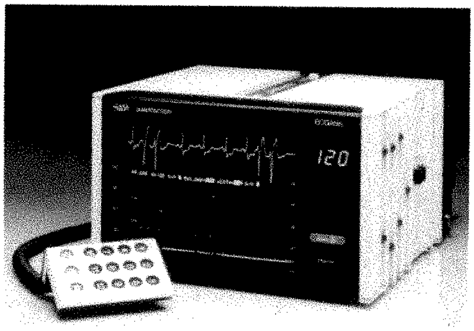

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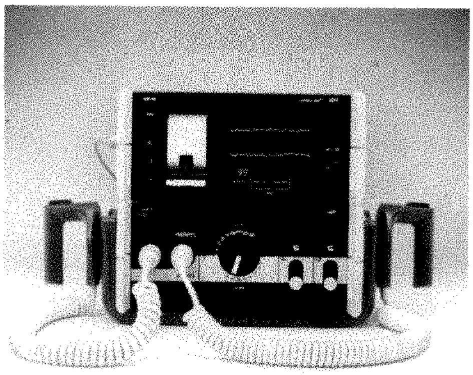

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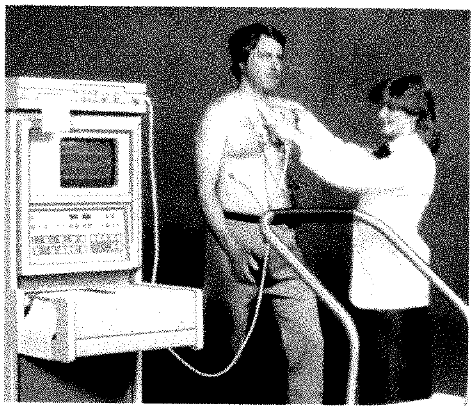

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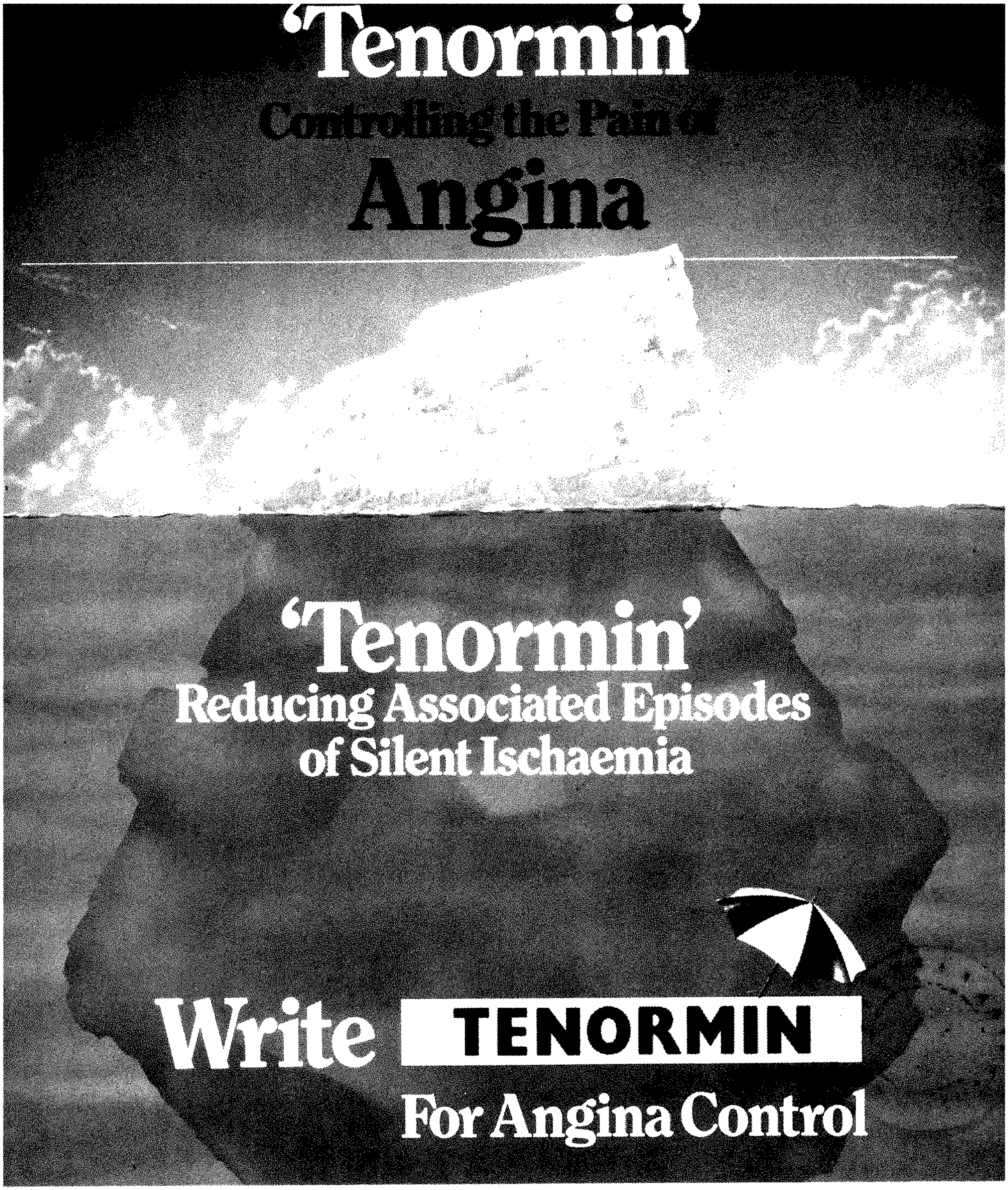

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British Heart Journal

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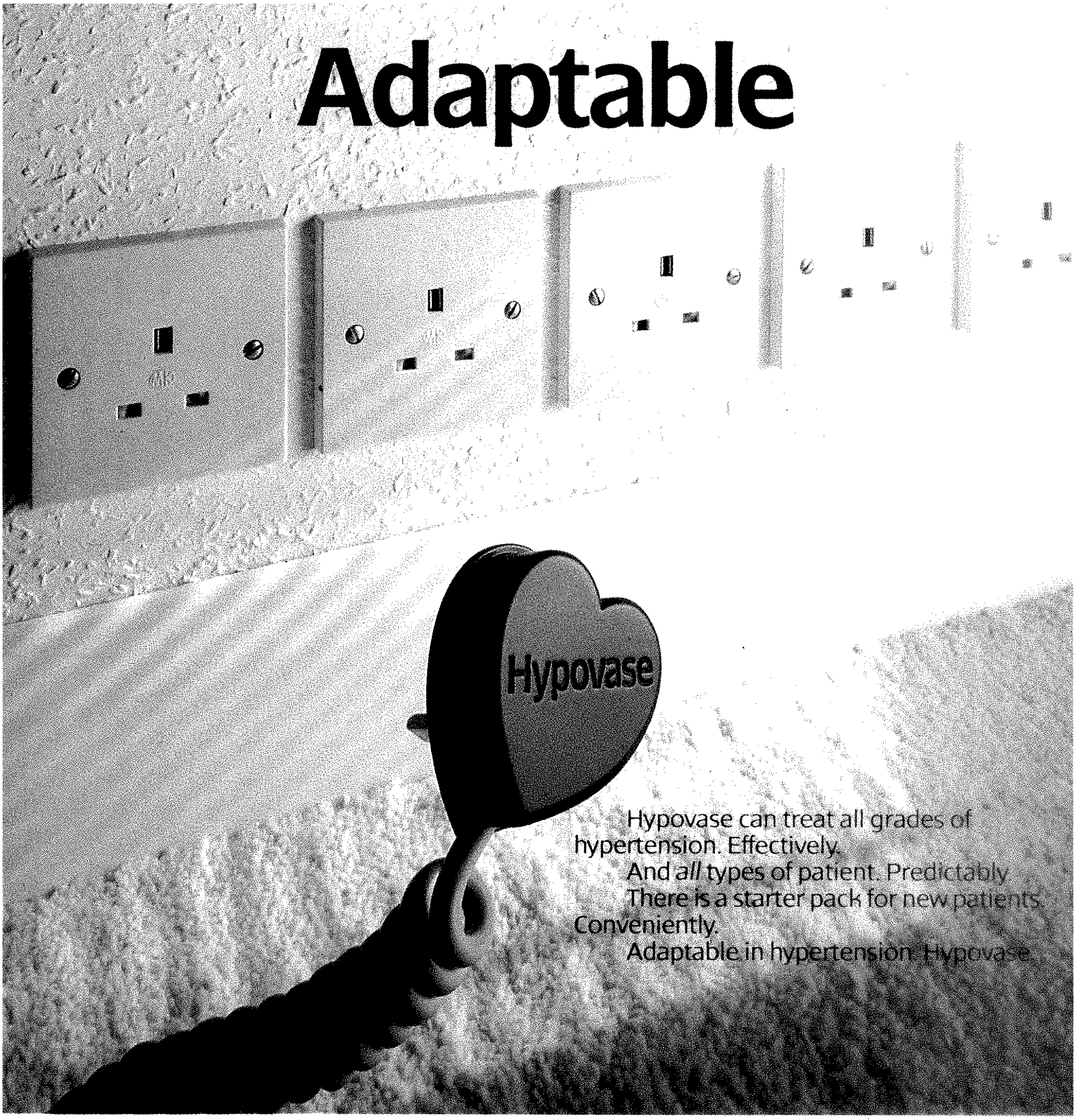

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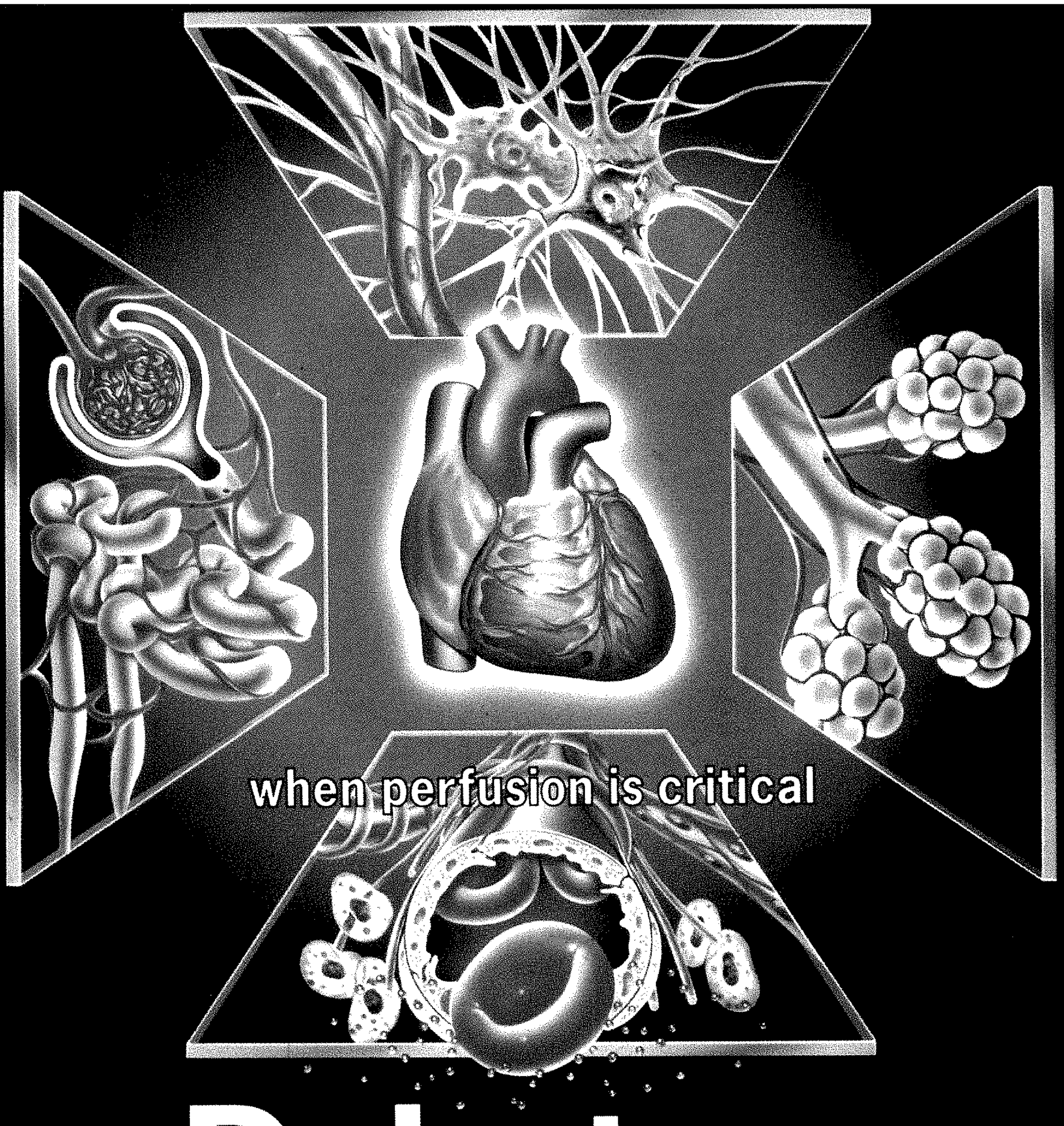

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Jubilee Editorial

Auscultation and phonocardiography: a personal view of the past 40 years

AUBREY LEATHAM

From the London, National Heart, and St George's Hospitals, London

The establishment of the British Cardiac Society coincided with and fostered the golden era of clinical cardiology that had started in the United Kingdom with Sir James Mackenzie and his school and reached its peak with Paul Wood in the 1950s. Factors known to me which influenced the spectacular advances in clinical diagnosis were the accuracy of postmortem examinations at the Bernhard Baron Institute of Pathology at the London Hospital under the direction of Professor Turnball (this was continued by Reginald Hudson at the National Heart Hospital and later by Michael Davies at St George's Hospital); accurate diagnosis by cardiac radiology led by John Parkinson; and the haemodynamic findings of right heart catheterisation which had been introduced by Cournand in the United States and by Sharpey-Schafer, McMichael, and Wood in England.

The first specialised cardiac department in a general hospital in England, and perhaps in the world, was started by Mackenzie at the London Hospital in 1911. He was followed by John Parkinson (later knighted for his service to medicine) in 1920, who all his life successfully fought to advance cardiology as a specialty. In 1931, with the help of the local traders and a gift of £500 from Queen Mary, a new cardiac department was opened at the London Hospital. In it Parkinson installed an *x* ray screening unit and pioneered the development of cardiac radiology. In 1947 one of his patients, William Sherbrook, left sufficient funds to start a new research fellowship and I was the first recipient.

In 1946 I was resident medical officer at the National Heart Hospital. John Parkinson and William Evans had been the mainstay of the hospital during the second world war and when I arrived at the end of the war I found a new atmosphere of questioning research which I had not encountered before. For example, I was perplexed by the variations in the clinical significance of hypertension and wondered whether examination of the fundi would help.I was immediately encouraged to start a survey of the clinical value of the retinal vessels in the assessment of hypertension and I spent many hours in the dark in Parkinson's screening room examining the fundi of his patients whom I was not allowed to examine in daylight lest the findings should bias my observations.

Auscultation and phonocardiography started for me with the gardener at the country branch of the hospital who while tending his plants was noticeably short of breath. When I examined him I found very abnormal heart sounds which I could not interpret. An earphone harnessed to the hospital string galvanometer electrocardiograph produced puzzling and large low frequency vibrations not at all resembling auscultation. A chest radiograph showed that he had an enormous heart; he died six months later and at necropsy proved to have Lutembacher's syndrome.

In 1947 as a specialist physician in the Army my main commitment was as mess secretary and I was therefore overjoyed to receive an offer from Parkinson and Evans to be the first Sherbrook Research Fellow at the London Hospital—I was informed that early release from the Army was available for research work (and coal mining). William Evans (fig 1) had made a start on recording heart sounds and murmurs using an old Cambridge double string galvanometer. His recordings were dominated by huge low frequency oscillations bearing no relation to the auscultatory findings (fig 2).

Rappaport and Sprague had shown in 1941 that considerable filtration of the low frequencies was required for the results of the phonocardiogram to resemble auscultation. This seemed to be the first step if the graphic recordings were to clarify and improve auscultation, which at that time was largely discarded as a scientific diagnostic method, an important reason being that Sir Thomas Lewis had little time for it. He had stated that the murmur of

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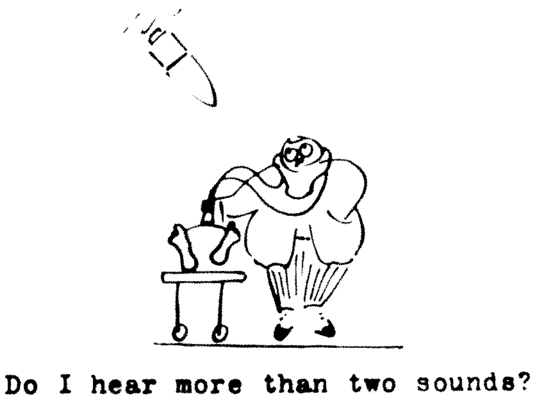

Do I hear more than two sounds?

Fig 1 *William Evans at work. A caricature which appeared in The London Hospital Gazette during the heavy bombing of London in 1941.*

mitral stenosis must be recognised by memorising its characteristics like the bark of a dog, and he and all the other senior physicians completely disregarded systolic murmurs. I was impressed by the American physiologist Wiggers who had demonstrated asynchrony between left and right ventricular pressure pulses and by Wolferth and Margolies who in 1935 had identified the two components of the second heart sound in bundle branch block by using a simultaneous carotid pulse, and had thereby reversed the electrocardiographic interpretation of the bundle affected. Dock had popularised the hypothesis that the opening and closing of valves was the major cause of heart sounds. It seemed to me that filtration of the low frequencies as described by Rappaport and Sprague would not only have the clinical advantage of producing results resembling auscultation, but should also show high frequency transients synchronising with valve movement (if this were the cause of the sounds) and would make identification of the components of sounds relatively easy. Fortunately, I was not aware that I would have to wait for thirty years for echocardiography to prove this correct.

Doctor Bernstein in the Physiology Department of the London Hospital made for us amplifiers with suitable filters, and Malcolm Towers and I started work on the second heart sound, because we could hear inspiratory splitting, just as described by Potain in 1866, and this seemed to be the first step in establishing that there was asynchronous contraction and relaxation of the two sides of the heart. I later realised that a study of the second heart sound was a particularly appropriate first step because James Hope, cardiologist to St George's Hospital, had been the first to show that the second heart sound was related to closure of the aortic and pulmonary valves. Using the double string galvanometer we made simultaneous phonocardiograms from the pulmonary area and mitral area together with an electrocardiogram or a recording of the carotid pulse. The first component of the second sound was the major one; it timed with the dicrotic notch of the carotid pulse, and was the sole component at the apex. The second component was confined to the pulmonary area and nearby (fig 3), and its delay during inspiration was the major cause of physiological splitting of the second sound. The weakness of our recording system was the tendency

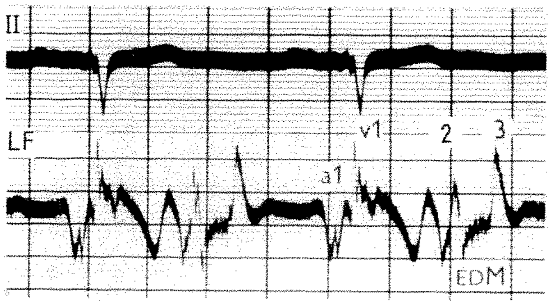


Fig 2 *Phonocardiography without filters as practised by William Evans in the early 1940s.*

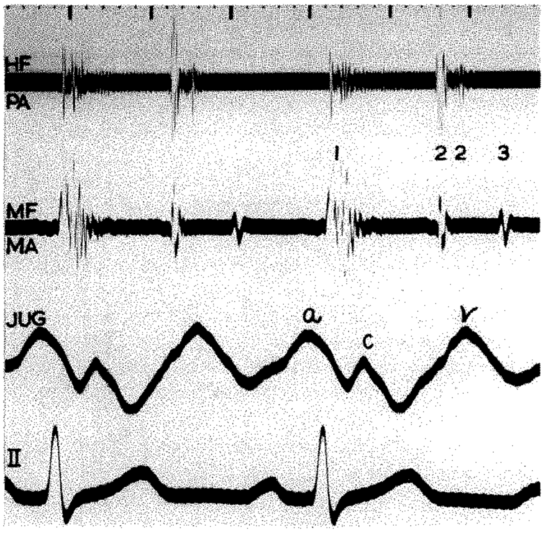


Fig 3 *Simultaneous phonocardiograms from the pulmonary area (PA) and mitral area (MA) showing that the later component of the second sound was confined to the pulmonary area. Filters were used to cut out the low frequencies and transmit the high frequencies so that the vibrations recorded resembled the results of auscultation through a rigid diaphragm chest piece (high frequency phonocardiogram (HF)), or through a bell (medium frequency phonocardiogram (MF)).*

for one string of our double string galvanometer to wrap itself around the other whenever we made a big deflection; this meant numerous trips to Cambridge in a 1934 baby Austin to visit an old technician who alone was able to unwrap the strings.

Elsewhere in Europe, and particularly in Sweden and Germany, the Mannheimer system with one microphone and multiple simultaneous channels each with a different frequency range was being developed, but nothing important was discovered with this technique (fig 4). Luisada in Chicago was using low frequency phonocardiograms (fig 5), bearing no relation to auscultation, and multiple timing channels with variable delays.

At the London Hospital cardiac radiology under Parkinson was making big advances. Each outpatient had to wait until the end of the afternoon for the *x* ray screening session and Parkinson's time in the dark room would probably last for about an hour with discerning and entertaining comment on almost every patient. With the help of the radiological findings described by Parkinson, Papp, and Bedford in 1939 in an early issue of the *British Heart Journal* it was now possible to diagnose atrial septal defect. Barber, Magidson, and Wood had described the signs and we were looking at the peculiar second

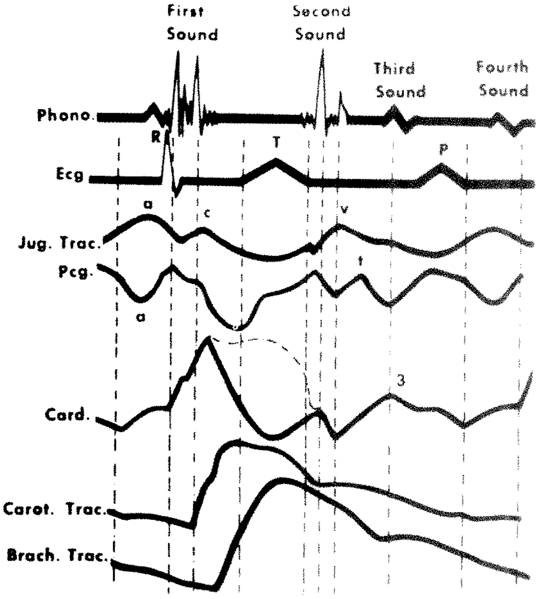


Fig 5 *One of Luisada's fine drawings of a single low frequency phonocardiogram with no accurate timing channel.*

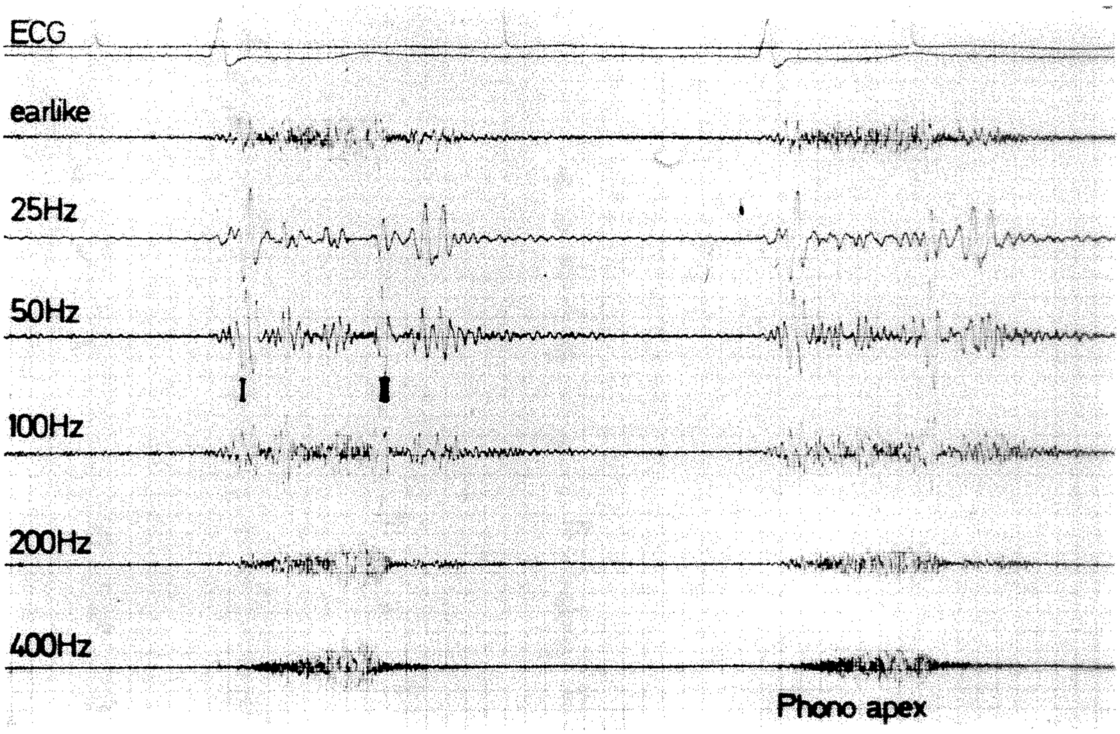
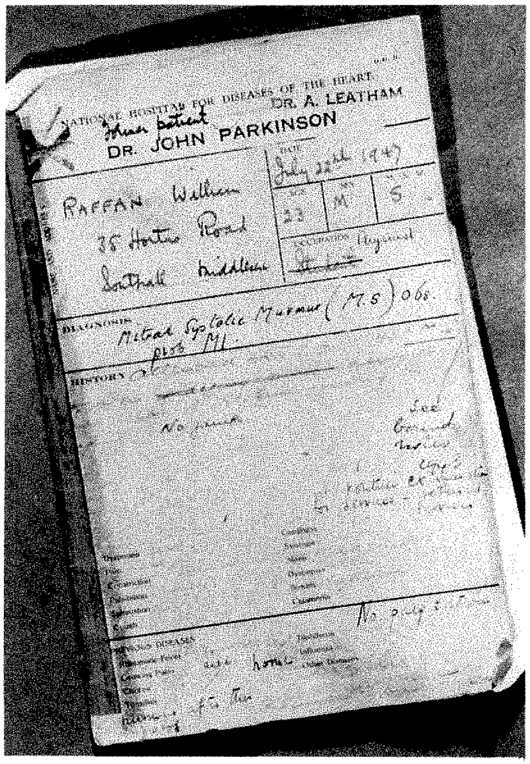


Fig 4 *Multiple recording with varying filtration taken from a single microphone as developed by Mannheimer.*

heart sound. It was Bill Dicks, our technician and collaborator at the London Hospital who said triumphantly one day, looking at the moving shadow of the string rather than at the finished graph, that the "split was fixed". Measurements proved him right, showing that both A_2 and P_2 were delayed nearly equally on inspiration. The description of reversed splitting of the second sound in left bundle branch block was an easy step from knowledge of physiological splitting. The discoveries that the delay of P_2 gave an exact estimate of severity of pulmonary stenosis and that the Eisenmenger ventricular septal defect and single ventricle gave a single sound had to wait for the stimulation of Paul Wood at the National Heart Hospital.

At the London Hospital the influence of Mackenzie, and now Parkinson, had resulted in systolic murmurs being almost ignored and certainly being regarded as unimportant. This was an overreaction to the diagnostic abuse and unnecessary cardiac invalidism (one of William Evans's famous phrases) that in earlier years had been prompted by the presence of a systolic murmur. Parkinson's reaction to a systolic murmur is demonstrated by the case notes (fig 6) of a patient with a systolic murmur (fig 7). (Indeed William Evans said of mitral incompetence that it was a description of the physician who diagnosed it; one wonders what he would say of mitral valve prolapse.) Thirty years later the patient with the systolic murmur died of coronary disease and proved to have mild rheumatic mitral regurgitation. It was soon clear from our high frequency phonocardiograms that the systolic murmur of aortic stenosis finished before the aortic component of the second heart sound, as indeed it had to, bearing in mind the cessation of forward flow before closure of the valve, and it seemed logical to describe these and similar murmurs as ejection murmurs. On the other hand, with mitral regurgitation the systolic murmur always reached A_2 and it was termed pansystolic, though sometimes it was almost confined or was confined to late systole. In this way apical systolic murmurs could be separated into left ventricular outflow ejection murmurs and mitral regurgitant murmurs; this was an important step forward in trying to produce order in a confused subject. With Wallace Brigden and the help of the Bernhard Baron Institute of Pathology we attempted an account of the course of mitral regurgitation. In ten necropsies of patients with severe mitral regurgitation there was only one with definite evidence of rheumatic valvulitis and in most of the others there was parachuting from an unknown cause, which we now appreciate was due to a floppy valve. From this background we could easily see in later years that Barlow's syndrome and mitral valve prolapse and the threat of sudden death would prove to be a fiasco in all but the most exceptional cases.

I moved in 1951 to the National Heart Hospital where Paul Wood was Director of the Institute of Cardiology. The chief technician John Norman found for me another 1918 Cambridge table model string electrocardiograph on which we mounted a second string and two mirror galvanometers with the aid of the Cambridge Instrument Company (fig 8). Each of the four galvanometers had a separate light source and these four sources had to be matched up to obtain an evenly illuminated recording; this was particularly difficult because the colour of the light sources varied. The falling plate camera used film, which was far superior to the usual recording paper because of its bigger density range. The length of the recording was limited to 15 cm, but the speed of fall of the plate could be varied infinitely to suit the requirements of the particular recording, and this system was ideal for composing a suitable length of recording to fit a page of the *Brit-*



NATIONAL HOSPITAL FOR DISEASES OF THE HEART

DR. A. LEATHAM

DR. JOHN PARKINSON

July 22nd 1947

RAFFAN William

23 M S

DIAGNOSIS Mitral Systolic Murmur (M.S.)

HISTORY

Fig 6 *Case notes of a patient seen by Parkinson in 1947. The only abnormal physical sign was an apical systolic murmur and it was inferred that he must have mitral stenosis (MS). Later, with some trepidation, I added MI (mitral incompetence).*

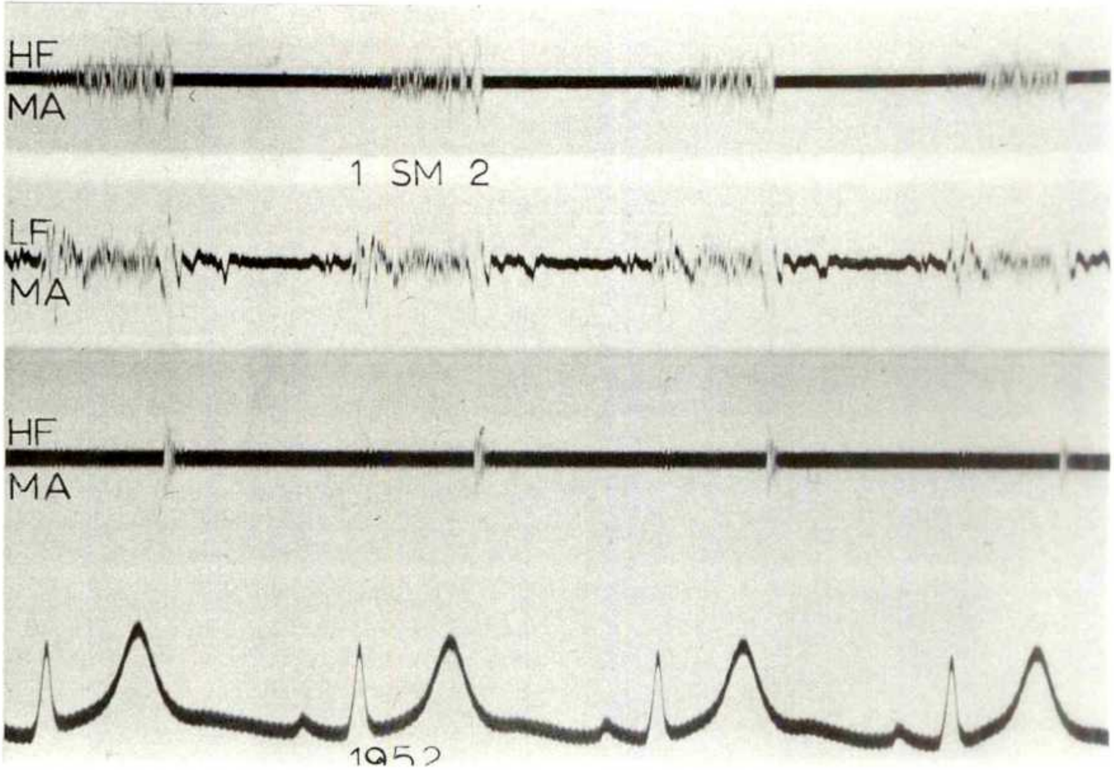


Fig 7 *Phonocardiogram of same patient in 1952 showing a pansystolic murmur and third sound.*

ish Heart Journal. The quality of the sound recordings made with this apparatus has never been surpassed (fig 9); it cannot even be equalled with modern apparatus.

The final and most difficult problem was identification of the components of the first heart sound and their separation from the early systolic ejection sounds. Right from the beginning of our recordings of the high frequency components of the first sound at the London Hospital it was clear that there were two components and, bearing in mind the precedence of left ventricular contraction over right, it seemed reasonable to guess that the first component arose from mitral valve closure and the second from tricuspid. Furthermore, the first component was by far the larger and was maximal at the apex, as befitting mitral closure, while the second was too late for mitral closure in relation to the carotid upstroke and was maximal at the lower left sternal edge over the tricuspid valve. Working with Edgar Haber, who was nearly as good at auscultation as at immunoassay, we had support for this concept by finding further delay in the second component with right bundle branch block, left ventricular ectopic complexes, and pacing with the electrode attached to the left ventricle. Opposition came from Luisada and his group in Chicago who could not record tricuspid closure with intracardiac phonocardiograms; also destruction of the right ventricle in dogs failed to alter the first sound which they thought came entirely from the left side of the heart. When they found that the pressure crossovers of the ventricles and atria occurred before the sound, they deduced that valve closure was noiseless. They were seemingly unaware of the lag between a pressure crossover and final halt of the valve. Even the Pittsburg group led by Shaver with superb sound pressure correlates denied a tricuspid origin to the second component of the first sound and attributed this sound to aortic ejection ("root sound"), even though the ejection sound in aortic stenosis was later and related to aortic valve opening.

We had to await echocardiography to obtain the exact timing of valve movement, but in the early days it was difficult to obtain reflection from the normal tricuspid valve and so we chose patients with Ebstein's anomaly and a large anterior leaflet of the tricuspid valve. The loud late component of the first sound, which we had assumed to be tricuspid closure delayed by the almost invariable right bundle

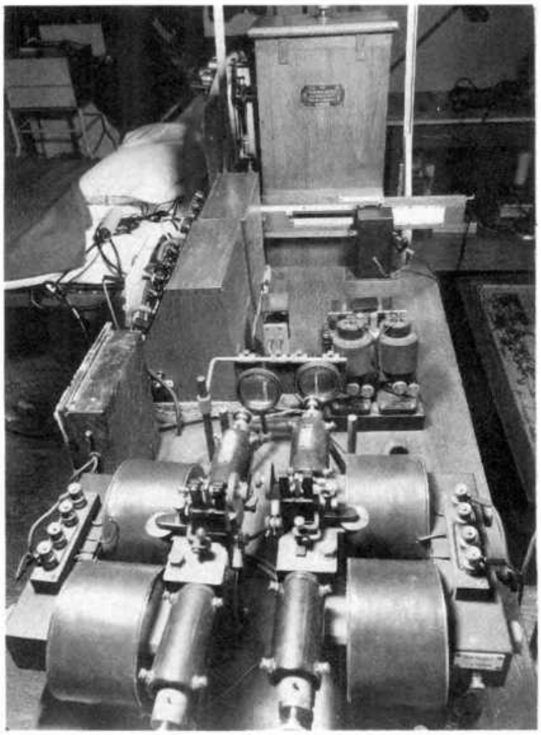


Fig 8 *The phonocardiograph used at the National Heart Hospital from 1952 onwards.*

branch block, was shown to coincide exactly with the final halt of the tricuspid valve on Dr Pridie's pioneering apparatus. Subsequently, with apparatus improved by Graham Leech, and simultaneously with Ernest Craige of Chapel Hill (and St George's Hospital), it was demonstrated that splitting of the first sound, as heard in most normal subjects by means of a rigid-diaphragm chest piece at the lower left sternal edge, was indeed due to mitral closure followed by tricuspid closure. There was synchrony between the final halt of the closing movement of the leaflets on the echocardiogram and the first component of the first heart sound and that of the closing tricuspid valve and the second component. This led to work with Nicholas Brooks and Mark Dancy on bundle branch block; it was confirmed that tricuspid closure was late in patients with isolated right bundle branch block; however, in patients with right bundle branch block and symptoms from generalised conducting tissue disease closure of the tricuspid valve was not delayed, indicating that the block was peripheral and occurred at arborisation level. This accorded with the site of histological change that was demonstrated by Michael Davies.

The mechanism causing variation in intensity of the first heart sound has been of interest for many years, and the relation to the PR interval was emphasised by Sam Levine of Boston, who during these times had done so much to stimulate clinical cardiology. I remember his discussing the mysteries of the first heart sound at the foot of the Mona Lisa in the Louvre during an early World Congress of Cardiology in Paris. Many years later, the advent of echocardiography showed conclusively that atrial contraction not only opened the atrioventricular valves, but also closed them (provided that the PR interval was long enough). Under these circumstances the first sound was soft. When the PR interval was short the valve was wide open at the onset of ventricular contraction and the first sound was loud. These observations were demonstrated clearly by Ernest Craige, but why should the distance of travel of this flimsy structure influence the intensity of sound produced by its final closure? From early days of phonocardiography it had been appreciated that the first sound was late as well as loud in mitral stenosis. It seemed to Brooks and I, and no doubt to many others, that lateness in mitral stenosis would put valve closure on a steeper part of the left ventricular pressure pulse so that the velocity of closure would be increased. We found with high speed echophonocardiography that the same principle applied to normal subjects. With a short PR interval the mitral valve, wide open at the moment of contraction, was late in reaching its final halting point and this coincided with a loud first sound. With a long PR interval the valve was nearly closed at the moment of ventricular contraction and its final movement and halt occurred at the beginning of ventricular contraction and coincided with a soft first sound.

Finally, a few words about early systolic sounds which Vogelpoel and I termed ejection sounds, despite the superb French expression "claguement protosystolique". Although the early ejection sound in pulmonary valve stenosis and the later ejection sound in pulmonary root dilatation from pulmonary hypertension with its prolonged ventricular isovolumic time had been useful in diagnosis, there was great debate about aortic ejection sounds. In the early days before the advent of echocardiography we were puzzled by the lateness of the aortic ejection sound which occurred during the upstroke of the aortic pressure pulse and not earlier when the valve opened. We had already used cineangiocardiography to examine the mitral valve and had showed that its final halt coincided with the loud first heart sound of mitral stenosis and we were contemplating a similar technique for the aortic valve when Richard Ross and O'Neil Humphries (exfellow from St George's) gave us the answer from

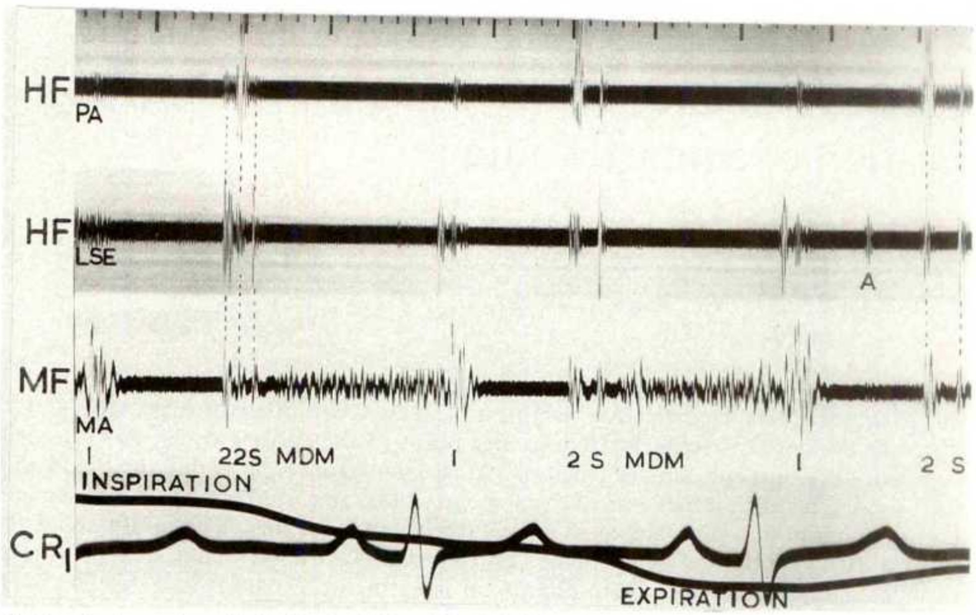


Fig 9 *Tracings taken with the National Heart Hospital phonocardiograph showing the value of simultaneous recordings from different areas in a patient with mitral stenosis. In the expiratory phase of respiration the snap (S) might have been P_2. In inspiration, however, the sequence of A_2, a loud P_2 (maximal in the pulmonary area), and a soft opening snap can be easily recognised. High frequency (HF) recordings from the pulmonary area (PA) and lower left sternal edge (LSE) and a medium frequency recording from the mitral area (MF) to show the mitral diastolic murmur (MDM). Nowadays, identification of sounds would have been achieved, perhaps more scientifically but not more clearly, by echophonocardiography.*

the Johns Hopkins Hospital. The sound coincided with the final halt of the upwardly moving valve visualised on the cineaortogram, a point now much more easily confirmed by echocardiography. Thus an aortic ejection sound is produced by movement of an abnormal valve, presumably one with abnormal prominence in systole so that it is carried rapidly upward by ejection, and the sound disappears if the valve is immobilised, particularly by calcium deposition. Aortic root dilatation by itself does not seem to produce a sound and the aortic "root sound" described by Shaver coincides with closure of the tricuspid valve on our high speed echocardiograms. Thus there seems to be no aortic parallel to the pulmonary root sound occurring with pulmonary artery dilatation (though we still do not know the mechanism of the ejection sound with the big aortic root of pulmonary atresia). In aortic regurgitation an ejection sound indicates an abnormal valve (most commonly bicuspid) rather than primary root dilatation which appears to be the commonest cause of aortic regurgitation in the United Kingdom. Recognition of aortic ejection sounds has also been of great value in studying the course of the bicuspid aortic valve and calcific aortic stenosis. A long follow up with Peter Mills of patients with isolated aortic ejection sounds has shown a bicuspid valve as the cause of the sound and in some patients we found that calcification and stenosis developed. We still do not know how often calcification develops and whether it can be prevented.

The evolution of ideas on the origins of heart sounds and murmurs is a striking example of the value of clinical research conducted over a long period of time. In this particular field at least, clinical research has yielded more information than isolated experiments in the laboratory.

I am grateful to Churchill Livingstone for permission to reproduce figs 3, 8, and 9a from *Auscultation of the Heart and Phonocardiography* by A Leatham, 1975.

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Magnetic resonance velocity mapping: clinical application of a new technique

S R UNDERWOOD, D N FIRMIN, R H KLIPSTEIN, R S O REES, D B LONGMORE

From the National Heart and Chest Hospitals, London

SUMMARY Magnetic resonance velocity mapping is a new technique which provides a display of velocity within the cardiovascular system at any point of the cardiac cycle. A short field echo sequence with even echo rephasing is used to obtain a signal from rapidly moving blood and a cine display is provided by rapid repetition of the sequence. The amplitude image shows the anatomy, with blood giving a high signal and areas of turbulent flow no signal. The phase image is a map of velocities at each point in the image plane. Thirteen cases are described in which the technique either provided a diagnosis or helped in functional assessment. Flow through atrial and ventricular septal defects was seen, although turbulent flow distal to the ventricular shunts led to some loss of quantitative information. In three patients with valve disease jets of abnormal flow were seen because of signal loss and it is suggested that the size of the area of turbulence may be used to quantify the severity of regurgitation. Velocities were measured in four coronary artery bypass grafts in two patients, and low velocity was seen in a graft with distal disease that supplied the infarcted territory. Velocity was reduced distal to an aortic coarctation and it was increased at the site of narrowing caused by thrombosis in a deep vein. The speed and direction of flow in the central vessels in a patient with complex congenital heart disease helped to establish the anatomy.

The technique provides useful information in a wide range of disorders of the cardiovascular system, and in some cases may avoid the need for invasive investigation.

Magnetic resonance imaging of the heart provides excellent anatomical detail because conventional sequences show a high contrast between flowing blood and other structures.[1-3] A wide variety of abnormalities can be studied including congenital disease,[4-6] myocardial disease,[7-9] and disease of the pericardium[10 11] and great vessels.[12-14] Cardiac function may also be studied by measuring chamber volumes at end diastole and end systole, and left and right ventricular stroke volumes, ejection fractions, and output can be calculated from these volumes.[15] These measurements are valuable in the assessment of valvar regurgitation[16] and atrial shunting,[17] but velocity mapping provides additional information which is useful in a wider range of conditions.

Moran *et al* first proposed encoding velocity in the phase of the magnetic resonance signal[18] and several groups subsequently acted on this suggestion.[19-22] The velocity map arises from a display of phase at each point in the image instead of the conventional display of amplitude, but a sequence that maintains the signal from flowing blood must be used. We have previously described a short field echo sequence with even echo rephasing which is suitable[23] and by comparing aortic flow measured from aortic velocity with that measured by left ventricular stroke volume we have shown the new method to be accurate in vivo.[24] Refinements of the technique include cine acquisition to provide information at all parts of the cardiac cycle and superimposition of colour coded velocities upon the conventional anatomical image to give an easily interpretable display of anatomy and flow.[25] Acceleration, may also be measured, and although this has important potential applications its clinical value is not yet established.

Requests for reprints to Dr S R Underwood, Magnetic Resonance Unit, The National Heart and Chest Hospitals, 30 Britten Street, London SW3 6NN.

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This paper is the first report of the clinical application of magnetic resonance velocity mapping. Thirteen patients are described in whom the technique was valuable either in establishing the initial diagnosis or in assessing the functional importance of the diagnosis.

Patients and methods

We used a Picker International Vista MR2055 magnetic resonance scanner operating at 0·5 T. For the anatomical images, electrocardiographic gating was used with two repetitions of 128 spin echo sequences (echo time 24 ms). The slice thickness was 10 mm and the images were displayed on a 256 × 256 matrix with a pixel size of 1·17 × 1·17 mm. The acquisition time was between three and four minutes depending upon heart rate, but two images were usually acquired synchronously (end diastole at one level with end systole at another).

Velocity mapping was performed using a field echo sequence with even echo rephasing (echo time 21 ms) and with gradient modifications to encode velocity in any of three orthogonal directions, either in the plane of the image or perpendicular to it. The slice thickness and resolution were the same as for the spin echo sequence. The sequence was repeated up to a maximum of 12 times per cardiac cycle with a reduced excitation pulse angle[26] in order to acquire information throughout the cycle. Magnitude reconstruction provided an anatomical image with high signal from blood (in contrast with the low signal obtained with conventional spin echo sequences), and phase reconstruction provided a map of velocity in the chosen direction after the phase map without velocity encoding had been subtracted to compensate for phase changes introduced by field inhomogeneity. To eliminate random phase values from background noise the velocity image was masked to show zero velocity in pixels with < 10% of maximum magnitude.

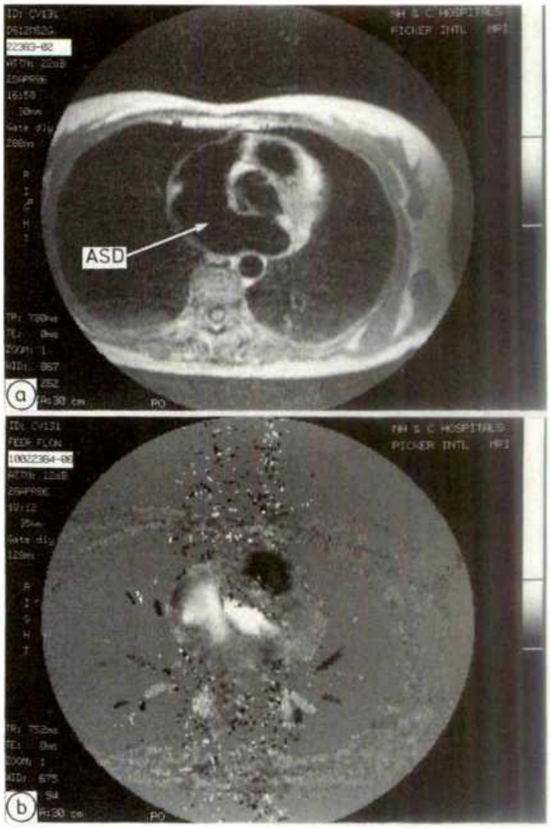

Fig 1 *(a) Transverse magnetic resonance image at mid-atrial level showing an ostium secundum atrial septal defect (ASD). The right atrium is dilated and right and left ventricular stroke volumes gave a pulmonary to systemic flow ratio of 2·1. (b) Mid-systolic velocity map of the same section coded from posterior to anterior. Zero velocity is shown in mid-grey, velocities from posterior to anterior in shades of light grey, and those from anterior to posterior in shades of dark grey. There is flow from left atrium to right atrium through the defect (light grey) as well as flow in the aortic root (white), pulmonary artery (black), and pulmonary veins.*

Table 1 *Magnetic resonance findings in five patients with intracardiac septal defects*

Patient		*Age*	*Abnormality*	*Findings*
1	F	47	Secundum ASD	Left to right flow through defect. No turbulent flow
2	F	17	Primum ASD with Dacron patch. Mild aortic coarctation	No flow through atrial septum. No turbulence within atria
3	F	17	Pulmonary atresia with homograft conduit. Subaortic VSD with Dacron patch but detached sutures	Dacron patch invisible. Left to right flow through VSD with downstream turbulence
4	M	46	Separate VSDs from LV to RV and LV to RA	Separate jets with downstream turbulence, the larger jet from LV to RA
5	M	15	Pulmonary atresia with pericardial conduit to hypoplastic PAs and systemic collaterals. Subaortic VSD	RV to LV flow through VSD. No turbulence

ASD, atrial septal defect; VSD, ventricular septal defect; LV, left ventricle; RV, right ventricle; RA, right atrium; PA, pulmonary artery.

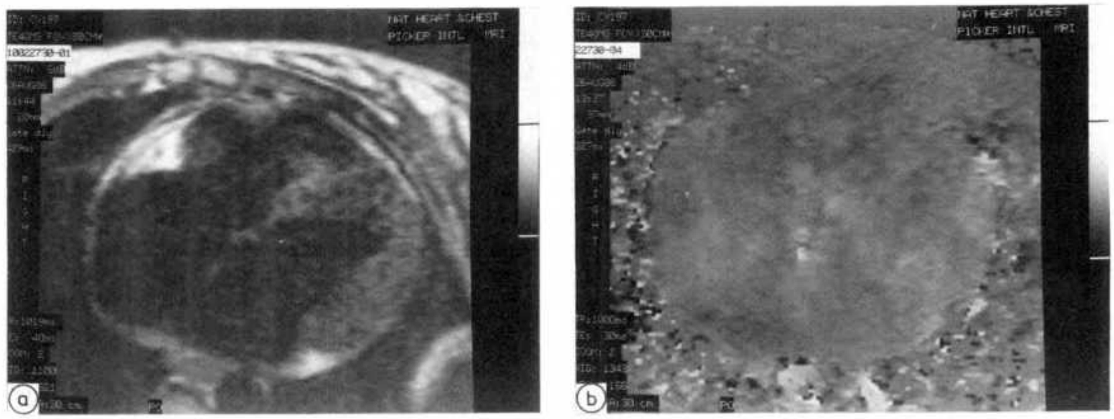

Fig 2 *(a) Transverse magnetic resonance image showing an ostium primum atrial septal defect that had been closed by a Dacron patch (not seen). (b) Velocity map encoded from posterior to anterior showing very low velocities in all chambers (mid-grey) and no flow between the atria in the region of the patch.*

Results

SEPTAL DEFECTS

Five patients with septal defects were studied (table 1). Patient 1 was initially thought to have either an atrial septal defect or pulmonary stenosis. Echocardiography was not able to demonstrate the atrial septum adequately but radionuclide angio-

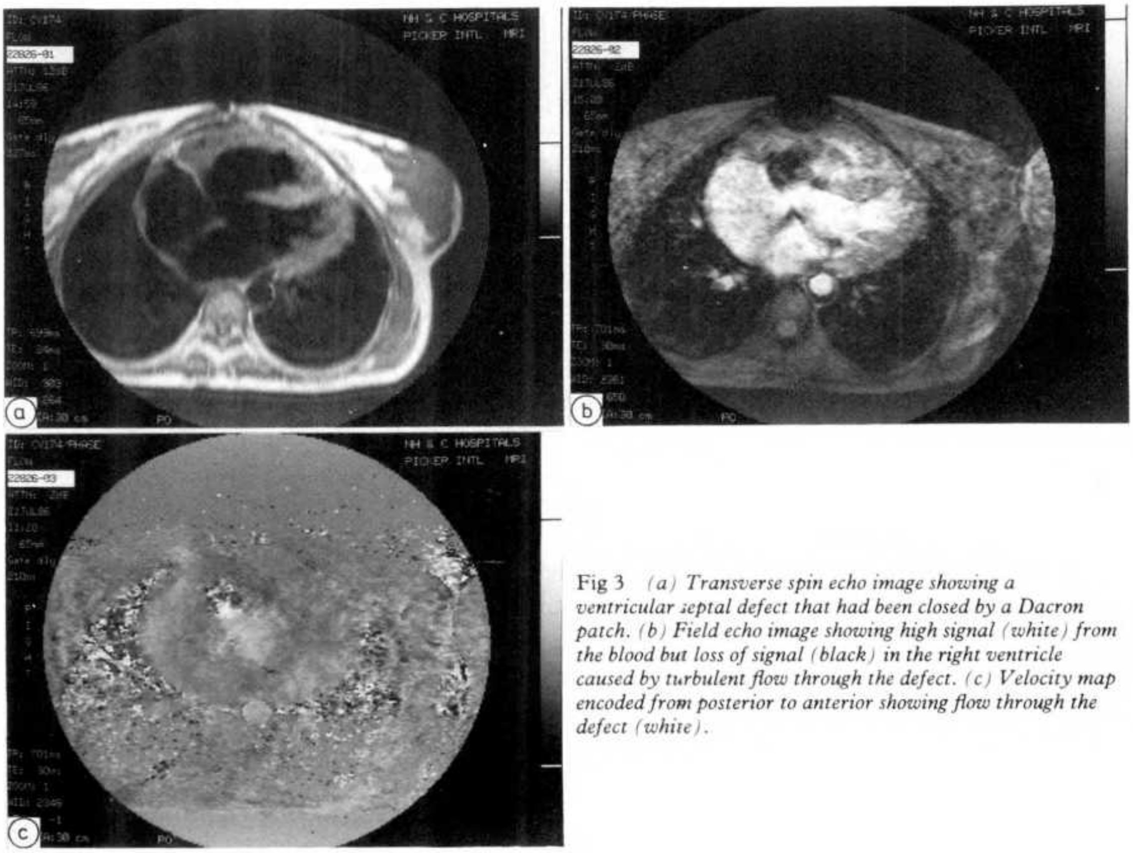

Fig 3 *(a) Transverse spin echo image showing a ventricular septal defect that had been closed by a Dacron patch. (b) Field echo image showing high signal (white) from the blood but loss of signal (black) in the right ventricle caused by turbulent flow through the defect. (c) Velocity map encoded from posterior to anterior showing flow through the defect (white).*

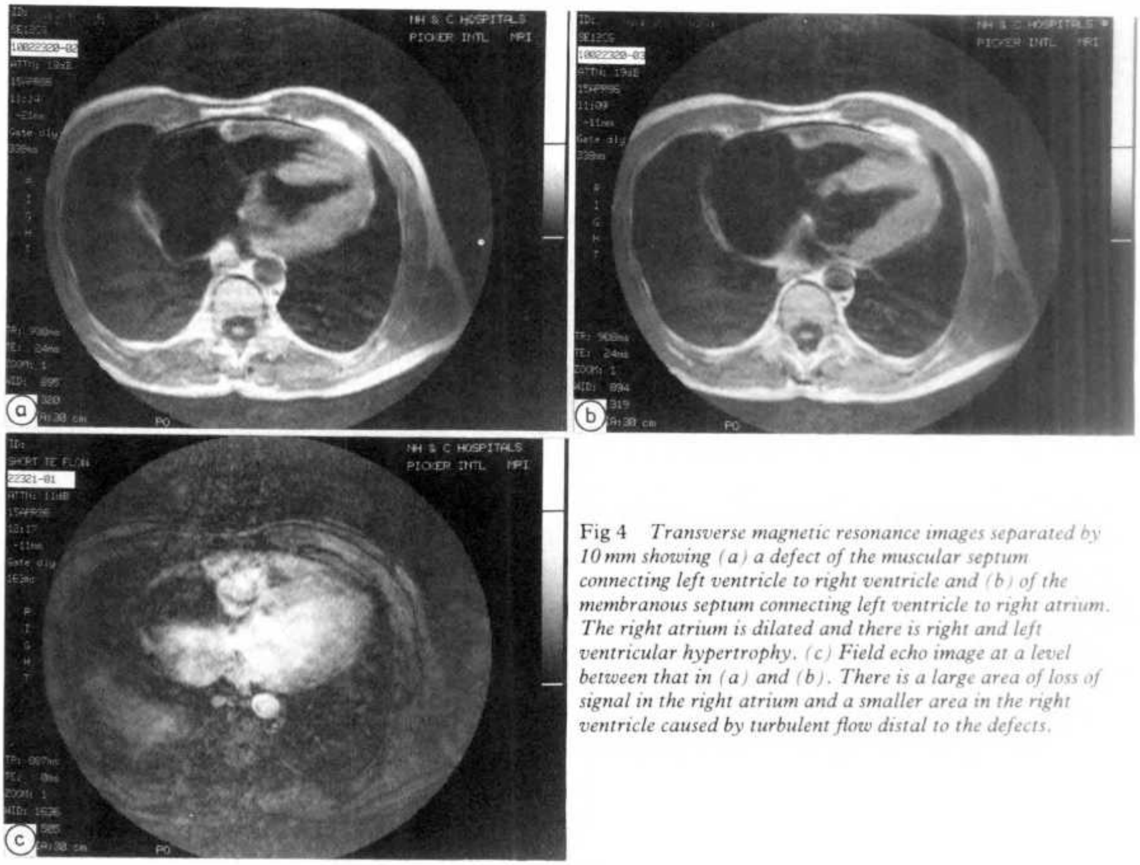

Fig 4 *Transverse magnetic resonance images separated by 10 mm showing (a) a defect of the muscular septum connecting left ventricle to right ventricle and (b) of the membranous septum connecting left ventricle to right atrium. The right atrium is dilated and there is right and left ventricular hypertrophy. (c) Field echo image at a level between that in (a) and (b). There is a large area of loss of signal in the right atrium and a smaller area in the right ventricle caused by turbulent flow distal to the defects.*

cardiography showed a left to right shunt with a pulmonary to systemic flow ratio of 2·3 and a left ventricular ejection fraction of 0·61. Magnetic resonance imaging showed an ostium secundum atrial septal defect and a dilated right heart (fig 1a) and from stroke volume measurements the pulmonary to systemic flow ratio was calculated to be 2·1. Figure 1b shows a mid-systolic phase map with velocity encoded from posterior to anterior. Flow velocities are seen on both sides of the defect passing from left atrium to right atrium, and the maximum velocity was 427 mm/s in early systole.

Patient 2 also had an atrial septum defect; this had been closed with a Dacron patch. Figure 2 shows the defect in transverse section and because Dacron gives no magnetic resonance signal the patch is invisible. The velocity map, however, shows no flow between the atria, so the patch can be assumed to be intact.

In contrast, patient 3 had a Dacron patch to a ventricular septal defect but the patch had become partially detached. There is an area of loss of signal in the amplitude image of the field echo sequence caused by turbulent flow (fig 3). This indicates the presence of a left to right shunt through the defect and although quantitative velocity information is lost in this region the size of the area of turbulence is considerable.

Patient 5 had separate defects between left and right ventricles and between left ventricle and right atrium (fig 4). The magnitude field echo image during systole showed a large area of loss of signal in the right atrium and a smaller area in the right ventricle, implying that a greater part of the left to right shunting was from left ventricle to right atrium. This was confirmed by cardiac catheterisation.

VALVAR HEART DISEASE

Three patients with valvar disease were studied (table 2). All three had areas of signal loss in the field echo amplitude images which led to loss of accurate velocity measurements, but because these areas corresponded to jets of abnormal flow useful information was still obtained. Figure 5 shows a patient with

Table 2 *Magnetic resonance findings in three patients with valve disease*

Patient		*Age*	*Abnormality*	*Findings*
6	F	57	Aortic stenosis (120 mm Hg gradient) and regurgitation (trivial)	Thickened valve doming in systole. Systolic turbulence in ascending aorta and small turbulent jet of regurgitation in diastole
7	F	39	Takayasu's arteritis. Severe aortic regurgitation	Thickened aortic wall. Large turbulent jet of regurgitation in diastole and minor peripheral turbulence in ascending aorta in systole
8	M	70	Prolapsing mitral valve, atrial fibrillation	Large area of turbulence in left atrium during systole arising from mitral valve

trivial aortic regurgitation and another with severe aortic regurgitation; the severity of regurgitation can be assessed from the area of signal loss in the regurgitant jet. In patient 6 turbulence distal to the stenotic valve led to loss of signal in the whole ascending aorta during systole and although there was some signal loss in patient 7 it was much less pronounced. Patient 8 had a floppy mitral valve and severe mitral regurgitation with atrial fibrillation, but despite the irregular rhythm the images were of sufficient quality to show a large area of turbulence in the left atrium from the mitral valve during systole.

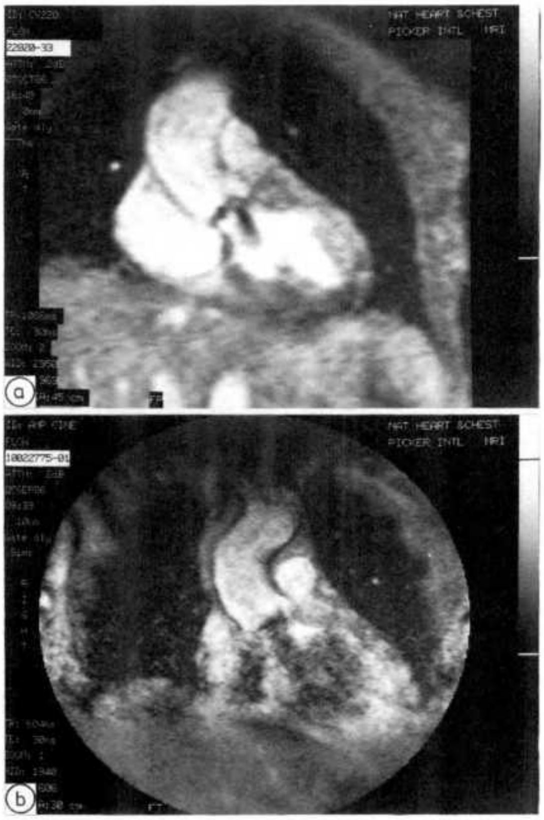

Fig 5 *(a) Diastolic coronal field echo image through the aortic valve in patient 6 with severe aortic stenosis and trivial regurgitation. The thickened valve appears as a black line and the regurgitation is seen as a small turbulent jet leading to loss of signal. (b) Equivalent image in patient 7 with severe regurgitation. The turbulent regurgitant jet is much larger.*

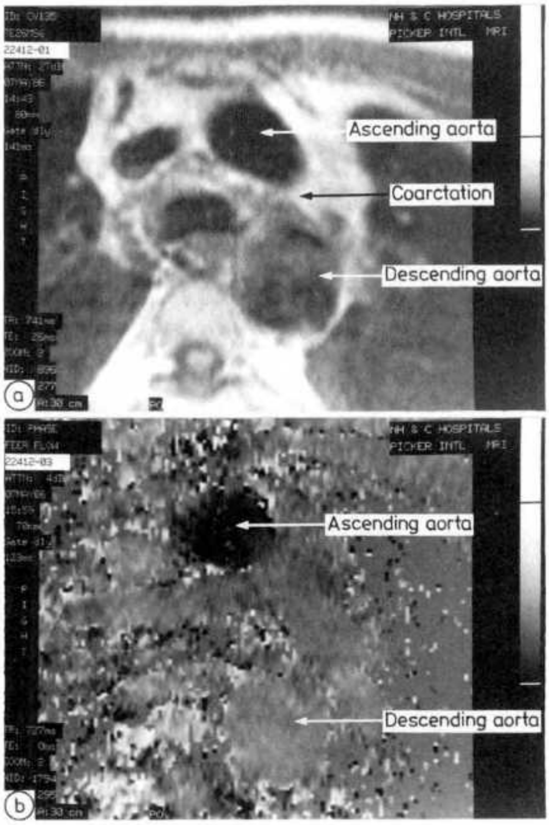

Fig 6 *(a) Transverse image through the aortic arch in mid-systole showing a coarctation. Signal from blood distal to the narrowing suggests slow flow. The right internal mammary artery is dilated. (b) Velocity mapping at a more caudal level showed peak velocities to be 406 mm/s in the ascending aorta (black) and 103 mm/s in the descending aorta (light grey).*

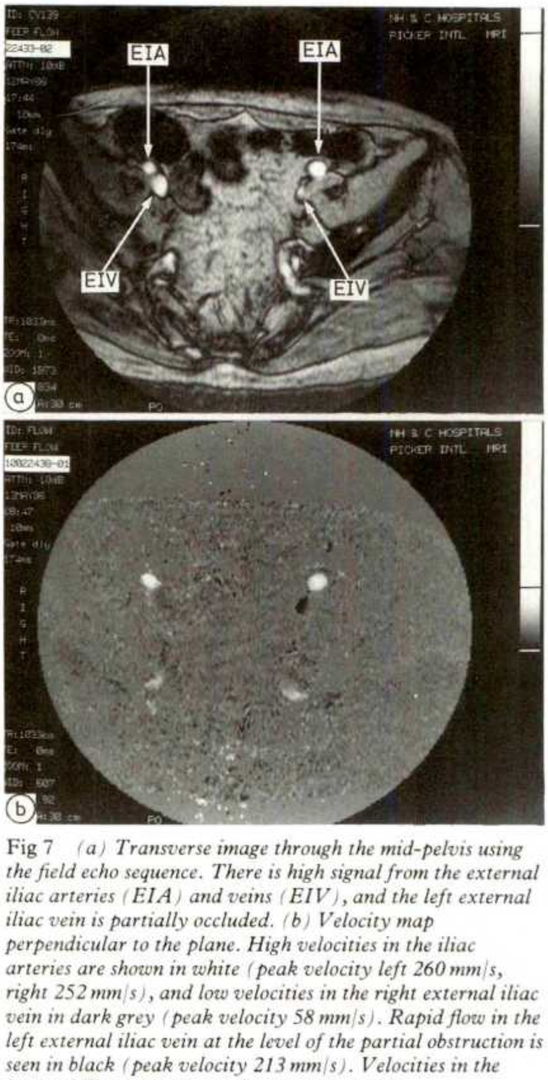

Fig 7 *(a) Transverse image through the mid-pelvis using the field echo sequence. There is high signal from the external iliac arteries (EIA) and veins (EIV), and the left external iliac vein is partially occluded. (b) Velocity map perpendicular to the plane. High velocities in the iliac arteries are shown in white (peak velocity left 260 mm/s, right 252 mm/s), and low velocities in the right external iliac vein in dark grey (peak velocity 58 mm/s). Rapid flow in the left external iliac vein at the level of the partial obstruction is seen in black (peak velocity 213 mm/s). Velocities in the internal iliac arteries are also seen posteriorly.*

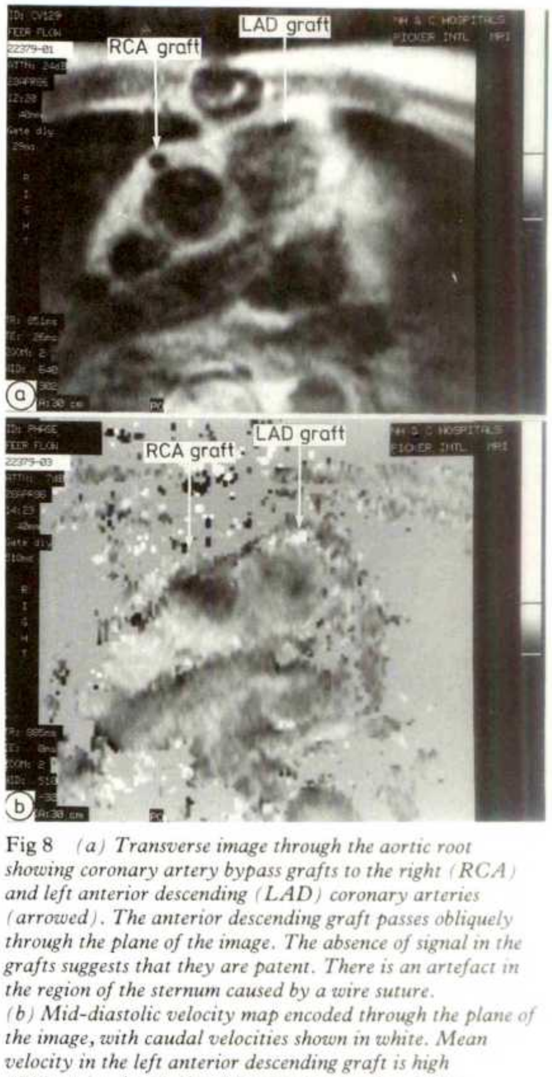

Fig 8 *(a) Transverse image through the aortic root showing coronary artery bypass grafts to the right (RCA) and left anterior descending (LAD) coronary arteries (arrowed). The anterior descending graft passes obliquely through the plane of the image. The absence of signal in the grafts suggests that they are patent. There is an artefact in the region of the sternum caused by a wire suture. (b) Mid-diastolic velocity map encoded through the plane of the image, with caudal velocities shown in white. Mean velocity in the left anterior descending graft is high (316 mm/s), but in the right coronary graft it is low (20 mm/s).*

AORTIC COARCTATION

A 50 year old man with hypertension and a Björk-Shiley mitral valve was thought clinically to have aortic coarctation but aortography failed to produce diagnostic images. Magnetic resonance imaging showed a tight constriction of the aortic arch at the level of the left carotid orifice and the right internal mammary artery was dilated (fig 6). The signal from blood distal to the constriction suggested slow moving blood, and velocity mapping showed a peak velocity of 406 mm/s in the ascending aorta (normal range 370 to 690 mm/s[24] but only 103 mm/s in the descending aorta (normal range 283 to 711 mm/s.[24] This low velocity confirmed the functional importance of the stenosis.

VENOUS THROMBOSIS

A 52 year old man with thromboangiitis obliterans (Buerger's disease) and a right below knee amputation developed a left sided deep venous thrombosis which was confirmed by venography. The signs resolved completely, and magnetic resonance imaging after recovery showed an irregular but patent left external iliac vein (fig 7). Velocity mapping showed high systolic velocities in the external and internal iliac arteries, and low velocities in the right external iliac vein. In the left external iliac vein at the level of the partial obstruction, velocity was high confirming that the narrowing was important.

CORONARY ARTERY BYPASS GRAFTS

The ability to measure velocities and hence flow within coronary artery bypass grafts is expected to be important in assessing function of the grafts. In one patient with grafts to the left anterior descending and circumflex territories, peak mid-diastolic velocities were 118 mm/s and 141 mm/s respectively. Both velocities are compatible with good flow[27] and accorded with findings at *x* ray arteriography.

In another patient, one graft was to the right coronary artery which was a small vessel with distal disease supplying previously infarcted territory, and the other graft was to a large anterior descending coronary artery. Both grafts had a signal void in the conventional spin echo images implying that they were patent (fig 8), but peak velocity was 316 mm/s in the left anterior descending graft and only 20 mm/s in the right graft.

CONGENITAL HEART DISEASE

A 15 year old girl had left isomerism with a common atrium, a ductus arteriosus, and pulmonary hypertension. She was reinvestigated because she had a pulmonary embolus shortly after appendicectomy and although ultrasound showed absence of the inferior vena cava, alternative venous drainage was not identified. Magnetic resonance imaging confirmed the cardiac anatomy and showed that the hepatic veins drained directly into the right atrium. A large left sided azygos vein was identified draining to a left sided superior vena cava and thence to a dilated coronary sinus. In the conventional images it was difficult to distinguish between the azygos vein and the descending aorta, but velocity mapping showed rapid caudal flow in the aorta (peak velocity 640 mm/s) and slower cranial flow in the vein (peak velocity 150 mm/s).

Discussion

Magnetic resonance was first used to measure blood flow in 1959 by Singer in the mouse tail.[28] Since then many different methods have been developed, but this technique is the first to have proved suitable for routine use. Methods based on time of flight between two planes produce semiquantitative measurements in blood vessels[29] but they are not applicable in the heart, and those based upon flow of blood into a magnetically saturated plane[30] are also difficult to quantify. Methods that use phase changes induced by motion along a field gradient have proved to be the most versatile within the cardiovascular system, but previous reports have been of the qualitative detection of flow only.[31] The ability to measure velocities within the cardiovascular system is likely to be useful in various situations and the cases we present have been chosen to illustrate this.

INTRACARDIAC APPLICATIONS

We have described the findings in five patients with septal defects. Conventional magnetic resonance imaging is sensitive in the detection of both atrial and ventricular defects[32 33] and although the left and right ventricular stroke volumes provide a measure of interatrial shunting, they are not helpful for the quantification of ventricular shunts, complex defects, or those associated with valvar regurgitation. Another limitation of conventional imaging is that the atrial septum is very thin in the region of the foramen secundum so that an apparent defect may be misleading and specificity is poor.[34] Oblique images and cine acquisition are helpful[35 36] but the detection of flow across a defect must be highly specific and velocity mapping is a useful addition to conventional imaging.

In some cases velocity measurements are complicated by the loss of the magnetic resonance signal. Absent signal from moving blood is beneficial in conventional imaging, but in velocity mapping it is important to avoid signal loss since velocity is encoded in the phase of the signal. The field echo sequence with even echo rephasing achieves this despite rapid movement of blood, but signal can be lost in the presence of turbulence and the ability to measure velocity is then lost. Despite this, the size of the area of signal loss may be helpful in assessing shunts and regurgitation,[37] although other factors such as the size and nature of the orifice and the pressure difference across it will also affect the degree of turbulence.

The loss of signal has several causes and there is not necessarily an exact correspondence between signal loss and turbulence. The main reason for this is the presence of different values of higher order terms of motion (such as acceleration) within a single pixel. This always occurs in turbulent flow and although it does not usually occur in the normal heart, it sometimes leads to signal loss during early diastolic filling through the mitral valve and around the periphery of the aortic root during systole.

The detection of turbulence is used in Doppler echocardiography where the severity of valvar regurgitation is assessed from the depth of penetration of the regurgitant jet into the upstream chamber.[38] Doppler ultrasound can also produce velocity maps[39] and it has some advantages over magnetic resonance: real time imaging is possible and turbulent flow does not lead to loss of information (although it may complicate interpretation). Important disadvantages are that it is less accurate,[40] high and low velocities are difficult to measure,[41] and access to the heart is limited, particularly for large posterior vessels.

VASCULAR APPLICATIONS

The cases of coarctation and venous thrombosis illustrate the potential applications of velocity mapping in the assessment of vascular disease. A velocity profile through a stenosis provides a measure of its functional importance and the pressure gradient across the stenosis can be estimated.[42 43] Conventional magnetic resonance imaging has already been used to assess peripheral vascular disease[44 45] but velocity and acceleration mapping will provide important additional information since it is the effect of disease upon perfusion that determines prognosis. Coronary artery bypass grafts have also been studied before but without velocity measurements,[46] and a comparison between velocity mapping and other measurements of graft function is now required. A combination of magnetic resonance angiography[47] with velocity and acceleration mapping offers the prospect of a completely non-invasive assessment of vascular disease.

We have validated velocity and flow measurements in phantom experiments, in the femoral artery, and in the ascending aorta[24] but velocity is only measured in a single direction in each velocity map and it is important to know the angle between the vessel and the plane in which it is imaged, or alternatively to make measurements in three orthogonal directions. For small vessels there are additional sources of inaccuracy such as the partial volume effect, and small vessels are best studied perpendicular to the plane of the image. Resolution may not yet be adequate for accurate flow calculations in coronary bypass grafts or coronary arteries but these preliminary results are encouraging.

Conclusion

Magnetic resonance velocity mapping is a new technique that provides a display of velocity within the cardiac chambers and major vessels at any point of the cardiac cycle. It is expected to be applicable in a wide variety of disorders of the cardiovascular system, and it may avoid invasive investigation in some cases. It is likely to be valuable in the assessment of intracardiac shunting, valve regurgitation and stenosis, and in the measurement of flow in congenital heart disease. Most exciting is its potential for the detection and assessment of vascular disease, including disease of the coronary arteries.

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References

1 Steiner RE, Bydder GM, Selwyn A, *et al.* Nuclear magnetic resonance imaging of the heart. Current status and future prospects. *Br Heart J* 1983; 50:202–8.
2 Lieberman JM, Alfidi RJ, Nelson AD, *et al.* Gated magnetic resonance imaging of the normal and diseased heart. *Radiology* 1984;152:465–70.
3 Higgins CB, Byrd BF, McNamara MT, *et al.* Magnetic resonance imaging of the heart: a review of the experience in 172 subjects. *Radiology* 1985;155: 671–9.
4 Fletcher BD, Jacobstein MD, Nelson AD, Riemenschneider TA, Alfidi RJ. Gated magnetic resonance imaging of congenital cardiac malformations *Radiology* 1984;150:137–40.
5 Fisher MR, Hricak H, Higgins CB. Magnetic resonance imaging of developmental venous anomalies. *Am J Roentgenol* 1985;145:705–9.
6 Didier D, Higgins CB, Fisher MR, Osaki L, Silverman NH, Cheitlin MD. Congenital heart disease: gated MR imaging in 72 patients. *Radiology* 1986;158: 227–35.
7 McNamara MT, Higgins CB, Schechtmann N, *et al.* Detection and characterisation of acute myocardial infarction in man with use of gated magnetic resonance. *Circulation* 1985;71:717–24.
8 Higgins CB, Lanzer P, Stark O, *et al.* Imaging by nuclear magnetic resonance in patients with chronic ischaemic heart disease. *Circulation* 1984;69:523–31.
9 Underwood SR, Rees RSO, Savage PE, *et al.* Assessment of regional left ventricular function by magnetic resonance. *Br Heart J* 1986;56:334–40.
10 Stark DD, Higgins CB, Lanzer P, *et al.* Magnetic resonance imaging of the pericardium: normal and pathologic findings. *Radiology* 1984;150:469–74.
11 Soulen RL, Stark DD, Higgins CB. Magnetic resonance imaging of constrictive pericardial disease. *Am J Cardiol* 1985;55:480–4.
12 Amparo EG, Higgins CB, Shafton EP. Demonstration of coarctation of the aorta by magnetic resonance imaging. *Am J Roentgenol* 1984;143:1192–4.
13 Glazer HS, Gutierrez FR, Levitt RG, Lee JKT, Murphy WA. The thoracic aorta studied by MR imaging. *Radiology* 1985;157:149–55.
14 McMurdo KK, de Greer G, Webb WR, Gamsu G. Normal and occluded mediastinal vessels: MR imaging. *Radiology* 1986;159:33–8.
15 Longmore DB, Klipstein RH, Underwood SR, *et al.*

Dimensional accuracy of magnetic resonance in studies of the heart. *Lancet* 1985;**i**:1360–2.

16 Underwood SR, Klipstein RH, Firmin DN, *et al.* Magnetic resonance assessment of aortic and mitral regurgitation. *Br Heart J* 1986;**56**:455–62.

17 Underwood SR, Klipstein RH, Firmin DN, *et al.* Magnetic resonance assessment of the accuracy of radionuclide methods for the quantification of valvular regurgitation and atrial shunting. In: Hoefer R, Bergman H, eds. *Radioactive isotopes in medicine and research.* Vienna: Verlag H Egerman, 1986;**17**:299–305.

18 Moran PR. A flow velocity zeugmatographic interlace for NMR imaging in humans. *Magnetic Resonance Imaging* 1982;**1**:197–203.

19 Bryant DJ, Payne JA, Firmin DN, Longmore DB. Measurement of flow with NMR imaging using a gradient pulse and phase difference technique. *J Comput Assist Tomogr* 1984;**8**:588–93.

20 Redpath TW, Norris DG, Jones RA, Hutchison JMS. A new method of NMR flow imaging. *Phys Med Biol* 1984;**29**:891–8.

21 van Dijk P. Direct cardiac NMR imaging of heart wall and blood flow velocity. *J Comput Assist Tomogr* 1984;**8**:429–36.

22 Moran PR, Moran RA, Karstaedt N. Verification and evaluation of internal flow and motion: true magnetic resonance imaging by the phase gradient modulation method. *Radiology* 1985;**154**:433–41.

23 Nayler GL, Firmin DN, Longmore DB. Cine MR blood flow imaging. *J Comput Assist Tomogr* 1986;**10**:715–22.

24 Longmore DB, Firmin DN, Nayler GL, Underwood SR, Klipstein RH. Cine magnetic resonance blood flow imaging in clinical use [Abstract]. *Magnetic Resonance Imaging* 1986;**4**:157.

25 Klipstein RH, Firmin DN, Underwood SR, Nayler GL, Rees RSO, Longmore DB. Colour display of quantitative blood flow and cardiac anatomy in a single magnetic resonance cine loop. *Br J Radiol* 1987;**60**:105–11.

26 Ernst RR. Sensitivity enhancement in magnetic resonance. *Advances in Magnetic Resonance* 1966;**2**: 1–135.

27 Underwood SR, Firmin DN, Klipstein RH, Rees RSO, Longmore DB. The assessment of coronary artery bypass grafts using oblique magnetic resonance imaging and velocity mapping [Abstract]. In: *Proceedings of the Fifth Annual Meeting of the Society of Magnetic Resonance in Medicine.* Berkeley: Society of Magnetic Resonance in Medicine, 1986;**5**:47–8.

28 Singer JR. Blood flow rates by nuclear magnetic resonance measurements. *Science* 1959;**130**:1652–3.

29 Feinberg DA, Crooks L, Hoenninger J III, Arakawa M, Watts J. Pulsatile blood velocity in human arteries displayed by magnetic resonance imaging. *Radiology* 1984;**153**:177–80.

30 Singer JR, Crooks LE. Nuclear magnetic resonance blood flow measurements in the human brain. *Science* 1983;**221**:654–6.

31 Wedeen VJ, Rosen BR, Chesler D, Brady TJ. MR velocity imaging by phase display. *J Comput Assist Tomogr* 1985;**9**:530–6.

32 Jacobstein MD, Fletcher BD, Goldstein S, Riemenschneider TA. Evaluation of atrioventricular septal defect by magnetic resonance imaging. *Am J Cardiol* 1985;**55**:1158–61.

33 Dinsmore RE, Wismer GL, Guyer D, *et al.* Magnetic resonance imaging of the interatrial septum and atrial septal defects. *Am J Roentgenol* 1985;**145**:697–703.

34 Lowell DG, Turner DA, Smith SM, *et al.* The detection of atrial and ventricular septal defects with electrocardiographically synchronised magnetic resonance imaging. *Circulation* 1986;**73**:89–94.

35 Feiglin DH, George CR, MacIntyre WJ, *et al.* Gated cardiac magnetic resonance structural imaging: optimization by electronic axial rotation. *Radiology* 1985;**154**:129–32.

36 Feiglin DH, Moodie DS, O'Donnell JK, Go RT, Sterba R, MacIntyre WJ. Evaluation of congenital heart disease by cine magnetic resonance imaging [Abstract]. *Eur J Nucl Med* 1985;**11**:A18.

37 Utz JA, Herfkens RJ, Heinsimer J, Glover GH, Pelc NJ, Shimakawa A. Rapid dynamic MR imaging of the heart in the evaluation of valvular function [Abstract]. *Radiology* 1986;**161**(P):198.

38 Nakagawa H, Yamamoto K, Takamiya M, Sakakibara H, Nimura Y. Semiquantitative grading of severity of mitral regurgitation by real-time two-dimensional Doppler flow imaging technique. *J Am Coll Cardiol* 1986;**7**:82–8.

39 Miyatake K, Izumi S, Shimizu A, *et al.* Right atrial flow topography in healthy subjects studied with real-time two-dimensional Doppler flow imaging technique. *J Am Coll Cardiol* 1986;**7**:725–31.

40 McLennan FM, Haites NE, Mackenzie JD, Daniel MK, Rawles JM. Reproducibility of linear cardiac output measurement by Doppler ultrasound alone. *Br Heart J* 1986;**55**:25–31.

41 Goldman ME. Real-time two-dimensional Doppler flow imaging: a word of caution. *J Am Coll Cardiol* 1986;**7**:89–90.

42 Hatle L, Brubakk A, Tromsdal A, Angelsen B. Non-invasive assessment of pressure drop in mitral stenosis by Doppler ultrasound. *Br Heart J* 1978;**40**:131–40.

43 Hatle L, Angelsen BA, Tromsdal A. Non-invasive assessment of aortic stenosis by Doppler ultrasound. *Br Heart J* 1980;**43**:284–92.

44 Herfkens RJ, Higgins CB, Hricak H, *et al.* Nuclear magnetic resonance imaging of atherosclerotic disease. *Radiology* 1983;**148**:161–6.

45 Wesbey GE, Higgins CB, Amparo EG, Hale JD, Kaufman L, Pogany AC. Peripheral vascular disease: correlation of MR imaging and angiography. *Radiology* 1985;**156**:733–9.

46 Jenkins JPR, Love HG, Foster CJ, Isherwood I, Rowlands DJ. Magnetic resonance imaging in the assessment of coronary artery bypass graft patency [Abstract]. *Br J Radiol* 1986;**50**:853–4.

47 Nayler GL, Firmin DN. Multislice MRI angiography [Abstract]. *Magnetic Resonance Imaging* 1986;**4**:156.

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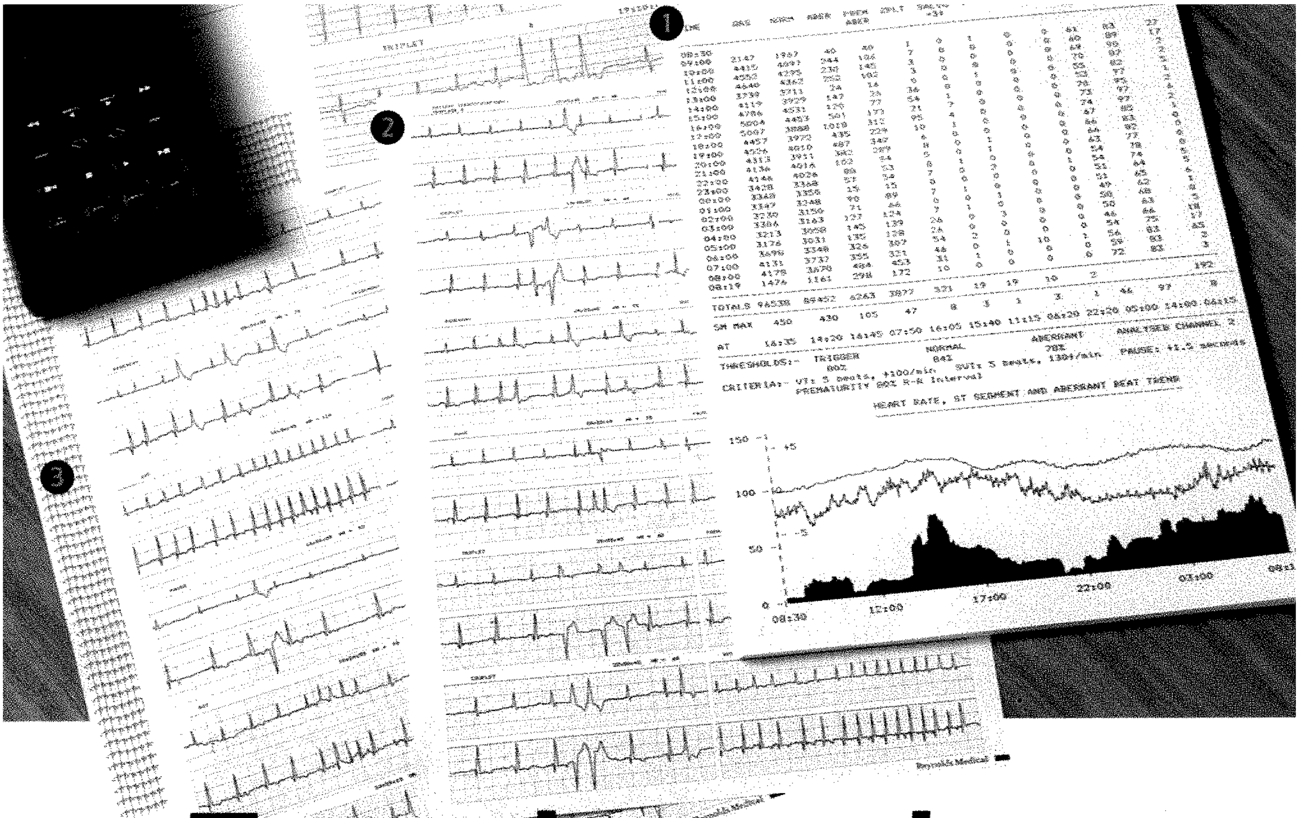

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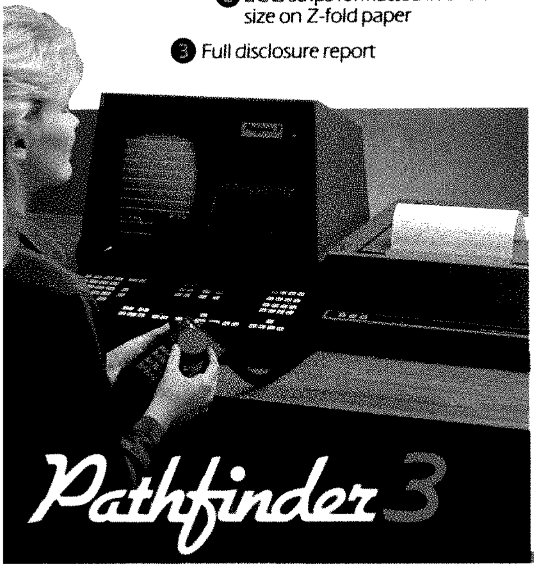

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Twenty year follow up of patients in the Medical Research Council trial of anticoagulants in acute myocardial infarction

A S DOUGLAS, LINDA COLWELL, GEOFFREY ROSE

From the Department of Medicine, Aberdeen Royal Infirmary and The Department of Epidemiology, London School of Hygiene and Tropical Medicine

SUMMARY A 20 year follow up of 1330 patients in the Medical Research Council trial of short term anticoagulant treatment in myocardial infarction showed no long term benefits; but it provided interesting data on the outcome in such patients. Sixteen per cent of the patients were alive 20 years later. The excess mortality rate in trial participants over that expected for England and Wales as a whole declined rapidly after the early months, but some excess persisted throughout the follow up. Three quarters of all the deaths were from coronary heart disease; 70% of these coronary deaths occurred after the patients had left hospital. This finding emphasises the importance of secondary prevention.

There has been little systematic study of the long term outcome after myocardial infarction.[1–7] A follow up of patients in the Medical Research Council trial of anticoagulants in acute myocardial infarction,[8] undertaken in order to check for any late effects of treatment, offered an opportunity also to examine survival over a 20 year period in a well-documented series of patients who had been discharged after a month of treatment. This seems to be the longest systematic follow up of survivors of myocardial infarction.

Patients and methods

Between 1963 and 1966 a total of 1416 patients with myocardial infarction (all ages, both sexes) entered the Medical Research Council trial and were randomly allocated to four weeks' treatment with phenindione, either full dosage or 1 mg daily. Their average age was 58 years; 77% were men. One hundred and fifteen patients in the high dose group died while they were in the trial compared with 129 in the low dose group; this difference was not statistically significant. Thromboembolism was significantly less common in the high dose group than in the low dose group (5% *vs* 11%).

With the help of the National Health Service central registers in Southport and Edinburgh and the Social Security office in Newcastle we were able to trace 94% of the patients (668 from the high dose group and 662 from the low dose group). Of these, 1111 (84%) had died and their death certificates have been made available.

The survival experience of the patients was compared with an expected survival curve based on the England and Wales life table for 1971,[9] and the application of appropriate age specific mortality rates to a cohort of the same age and sex distribution as the patients in the study. Eleven patients entered the trial more than once; their survival experience has been reckoned from the first attack.

Results

Figure 1 shows the 20 year progress of coronary heart disease mortality for the trial's two groups: the differences are small and within chance limits. Results for specific causes of death were also similar in the two groups.

Despite having suffered a major acute episode in a dangerous chronic disease, 219 (16%) patients are alive 20 years later. For those who survived for 28 days the 20 year survival rate was 20%; however,

Requests for reprints to Professor Geoffrey Rose, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT.

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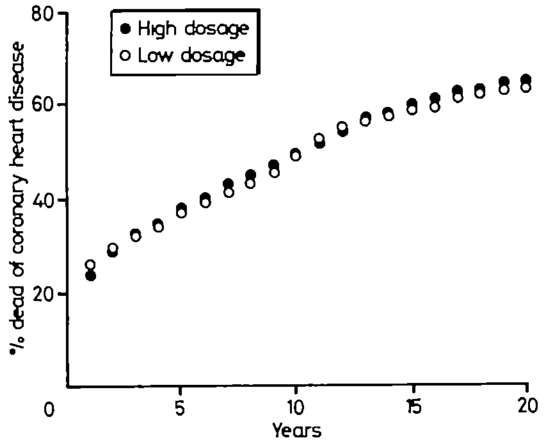

Fig 1 *Cumulative deaths (%) from coronary heart disease in patients allocated to high and low dosage anticoagulant treatment for a month.*

58% of them (629 out of 1088 discharged alive from hospital and not lost to follow up) have died of the same disease. The distribution of the remaining causes of death is similar to that in the general population (table).

Figure 2 shows the actuarial mortality curves for the patients, compared with the experience of the general population of England and Wales,[9] adjusted for age and sex. Clearly the worse experience of the patients arises chiefly in the first five years, and especially the first year. The excess mortality in relation to the general population is 2·3 in the first 10 years and 1·4 in the next 10 years.

Table *Twenty year mortality in 1416 patients admitted to hospital with myocardial infarction*

Status	*Number (%)*
Alive	219 (16)
Dead.	
Coronary heart disease: in hospital	223 (17)
subsequently	629 (47)
Stroke	41 (3)
Other cardiovascular disease	50 (4)
Lung cancer	31 (2)
Other respiratory disease	48 (4)
Other cancer	33 (2)
Diabetes mellitus	12 (1)
Other cause	30 (2)
Cause unknown	14 (1)
Lost to follow up	86

Survival was less likely in women than men (20 year survival 13·2% compared with 17·4%), but they were an older group (average age at entry 62 years compared with 56 years for men).

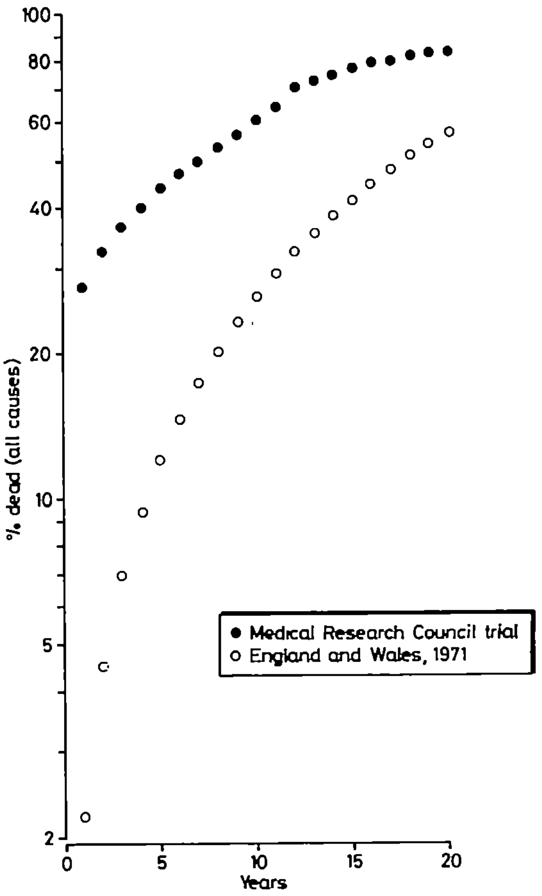

Fig 2 *Cumulative actuarial mortality from all causes in study patients compared with expected mortality according to England and Wales rates (semilogarithmic scale).*

Discussion

The trial did not identify any significant reduction in coronary events during the short period of anticoagulant treatment, despite the convincing evidence of a short term reduction in thromboembolic events; and it is therefore not surprising that no long term benefit has emerged. A subsequent pooling of results from six randomised trials found an overall significant reduction of 21% in the acute case fatality.[10] Thus the difference in the Medical Research Council trial result could be due to chance.

As far as we know, 20 years is the longest period during which survivors of hospital admission for myocardial infarction have been studied; the cases were all well documented and had no major criteria for exclusion. Success in tracing 94% of the patients

20 years later demonstrates the particular advantages enjoyed by investigators who study the long term outcome in patients in the United Kingdom, even where such a long follow up was not planned at the outset.

Several important conclusions follow from the findings. The first is that for a substantial proportion of patients suffering a myocardial infarction, outcome is favourable: of those who survived the acute attack one in five are alive 20 years later. The average age of these patients was already 58 years at entry to the study. Their excess risk declined progressively with increasing interval from the attack, and after 10 years it was small. In interpreting the changing slopes of the survival curves it must, however, be remembered that they refer to a changing study population. The declining risk reflects not only the lengthening interval from the attack but also the progressive disappearance of those who were older at the time of the attack. Those who survive are, however, getting older and other things being equal this would increase their risk of death.

Norris's group have shown that impairment of left ventricular function influences long term as well as short term prognosis,[1] implying that among those with lesser degrees of myocardial injury the long term prognosis is even better than our figures suggest.

The second important conclusion is that myocardial infarction is a chronic and protracted disease. In our study of hospital patients with myocardial infarction more than 70% of all the deaths attributed to coronary heart disease occurred more than a month after hospital admission. This illustrates how the acute care of coronary patients touches on only a small part of the total problem, and it emphasises the much greater potential importance of secondary prevention. In this series, for example, a 10% reduction in coronary mortality after discharge would have been equivalent to a 25% reduction during the period in hospital. After the attack there is a rapid decline in the death rate of these patients; but this should not distract attention from the fact that most of the deaths occur after patients have left hospital and that such patients continue to be at high risk

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References

1 Merrilees MA, Scott PJ, Norris RM. Prognosis after myocardial infarction: results of 15 year follow up *Br Med J* 1984;**288** 356–9.

2 Weinblatt E, Shapiro S, Frank CW, Sager RV. Prognosis of men after myocardial infarction. mortality and first recurrence in relation to selected parameters. *Am J Public Health* 1968;**58** 1329–47.

3 Pell S, D'Alonzo CA. Immediate mortality and five year survival of employed men with a first myocardial infarction. *N Engl J Med* 1964;**270**:915–22

4 Honey GE, Truelove SC. Prognostic factors in myocardial infarction. *Lancet* 1957,**i**.1155–61, 1209–12.

5 Cole DR, Singian EB, Katz LN. The long term prognosis following myocardial infarction and some factors which affect it. *Circulation* 1954;**9**:321–34.

6 Katz LN, Mills GY, Cisneros F. Survival after acute infarction. *Arch Intern Med* 1949,**84**.305–20.

7 Levine SA, Rosenbaum FF Prognostic value of various clinical and electrocardiographic features of acute myocardial infarction· ultimate prognosis. *Arch Intern Med* 1941;**68**:1215–31.

8 Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council 1969. Assessment of short-term anticoagulant administration after cardiac infarction. *Br Med J* 1969;**i**:335–42.

9 The Registrar General's Decennial Supplement for England and Wales. *Life tables 1970–1972.* (Series DS no. 2.) London: HMSO, 1979.

10 Chalmers TC, Matta RJ, Smith H, Kunzler AM Evidence favoring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med* 1977;**297**:1091–6.

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Follow up results of treatment of unstable angina by coronary angioplasty

GIUSEPPE STEFFENINO, BERNHARD MEIER, LEO FINCI, WILHELM RUTISHAUSER

From the Cardiology Centre, University Hospital, Geneva, Switzerland

SUMMARY Eighty nine of 327 consecutive patients undergoing coronary angioplasty at a centre had unstable angina—defined as either a worsening of the frequency or the severity of chest pain or severe episodes of chest pain at rest with no evidence of acute myocardial infarction. Multivessel disease was present in 31 of these patients. Two or more vessels were dilated in the same procedure in one fifth of the patients. Primary success was obtained in 80 (90%) patients. Acute myocardial infarction was a complication in four (5%) patients, including two of four patients who needed emergency coronary bypass grafting. Follow up coronary angiography at a mean (SD) of 10 (6) months in 57 patients showed restenosis in 21 (37%): of these, 13 patients had repeat coronary angioplasty and three had elective coronary bypass grafting. All patients in whom angioplasty was initially successful were followed up for 10 (6) months after the last angioplasty procedure. There were no deaths. One patient had sustained a myocardial infarction unrelated to the dilated vessel. Clinically, 74 patients improved by at least one New York Heart Association class and 40 (50%) were symptom free and with no signs or symptoms of myocardial ischaemia on a stress test.

Coronary angioplasty offers long term symptomatic improvement at an acceptable risk in the majority of patients with unstable angina.

Patients with unstable angina are at increased risk of myocardial infarction and premature death.[1] In the past 10 years there has been much discussion on the best way to manage such patients.[2 3] Although chest pain is often controlled by bed rest and intensive medical treatment, a substantial percentage of patients none the less have early unfavourable outcomes on medical treatment alone[4]; this result is partially related to persistent silent ischaemia.[5] Percutaneous transluminal coronary angioplasty is increasingly accepted as a form of revascularisation in patients with unstable angina.[6–12] We report the results of a follow up of selected patients with unstable angina treated with coronary angioplasty.

Patients and methods

Between July 1983 and May 1985 a total of 327 patients underwent coronary angioplasty at our centre. Eighty nine patients had unstable angina—defined as either a worsening in the frequency or severity of chest pain or severe episodes of prolonged pain at rest shortly before admission with no electrocardiographic or enzymatic evidence of acute myocardial infarction. We studied 76 (85%) men and 13 women (mean (SD) age 55 (9) years). In 54 patients there was a history of old myocardial infarction. There was two and three vessel disease

Baseline clinical and angiographic data in patients treated with angioplasty

Variable	*Data*
Patients	89
Age (years)	55 (9) (35–69)
Men	85%
Left ventricular ejection fraction (%)	62 (11) (41–80)
Old myocardial infarction	54 (61%)
One vessel disease	58 patients
Two vessel disease	22 patients
Three vessel disease	9 patients

Requests for reprints to Dr Bernhard Meier, Centre de Cardiologie, Hôpital Cantonal Universitaire, CH 1211, Geneva, Switzerland

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causing stenosis of 70% of the luminal diameter in 22 and nine patients respectively. Four (5%) patients had had previous coronary angioplasty. The table summarises the baseline clinical and angiographic data. Patients were treated with nitrates, β blockers, calcium antagonists, and aspirin. The degree of coronary stenosis was visually estimated as a percentage of the luminal diameter by two angiographers in multiple projections and results were averaged.

Coronary angioplasty was performed as previously described,[13] after intravenous heparin (10 000 IU) and intracoronary isosorbide dinitrate (0·2 mg) or nifedipine (0·1 mg) or both. The transfemoral approach was used in all cases. Prolonged anticoagulation with intravenous heparin infusion was not used routinely after a successful procedure, but the patients received oral nifedipine 40 to 60 mg/day and aspirin 100 mg/day unless contraindicated. Primary success was considered to have been achieved if the following conditions were met: angiographic improvement of the lesion with no significant residual stenosis, improvement in the transstenotic pressure gradient (whenever available), absence of electrocardiographic or enzymatic evidence of myocardial infarction or need for coronary artery bypass grafting within 48 hours of the procedure, and improvement of at least two New York Heart Association functional classes for angina. In multivessel angioplasty success was defined as dilatation of at least the ischaemia related lesion. Transient electrocardiographic changes in leads V1–V5 were regarded as indicating lesions of the left anterior descending coronary artery, while changes in leads V6, I, aVL or II, III, and aVF were said to reflect a lesion in either the circumflex or the right coronary artery respectively. When no electrocardiographic changes had been recorded, the vessel that showed the most severe stenosis and perfused a myocardial region with at least partially preserved contraction was identified as the ischaemia related vessel. Treatment with aspirin 100 mg/day was recommended to all patients after discharge and antianginal, hypotensive, or antiarrhythmic drugs were also given as clinically indicated.

The clinical follow up consisted of an interview, a physical examination, and a symptom limited stress test. The stress test was performed on a bicycle ergometer. The workload was increased by 25 W every three minutes, and the test was regarded as positive if the patient complained of typical chest pain or if ST segment depression of $\geqslant 1$ mm appeared 0·08 s after the J point. A few patients lived a long way from the hospital and they were followed up by a questionnaire or a telephone interview.

We recommended that all patients should have follow up coronary angiography. Recurrence of stenosis was defined as loss of $\geqslant 50\%$ of initial gain in luminal diameter at the site of angioplasty. When appropriate the χ^2 test was used for statistical analysis. A p value $< 0{\cdot}05$ was regarded as significant.

Results

Coronary angioplasty was attempted in 89 patients and was successful in 80 (90%). In 18 (20%) patients we were able to attempt coronary angioplasty on the same day as diagnostic coronary angiography. In 18 (20%) patients two or more vessels were dilated during the same procedure (fig 1). Lesions of the left anterior descending coronary artery accounted for 54% of the 110 dilated vessels (fig 2). The mean (SD) diameter of stenosis was reduced from 84 (12)% to 25 (10)% and the mean transstenotic pressure gradient (available for 82 successfully

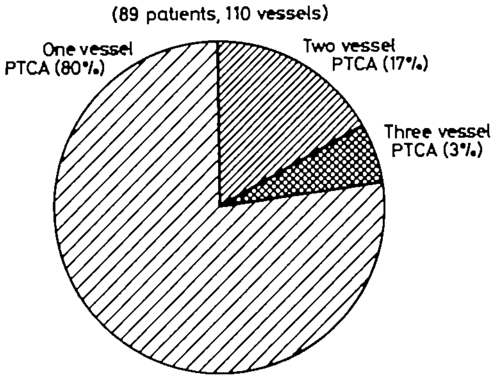

Fig 1 *Distribution of single and multivessel coronary angioplasty procedures. PTCA, percutaneous transluminal coronary angioplasty.*

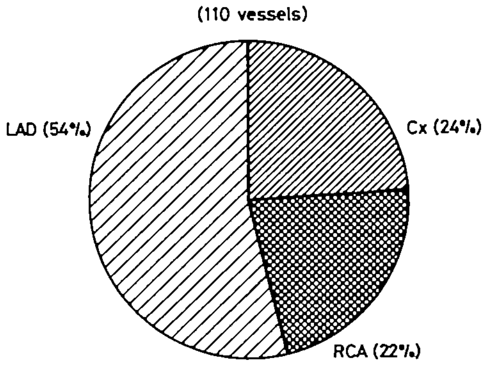

Fig 2 *Distribution of vessels attempted. LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery.*

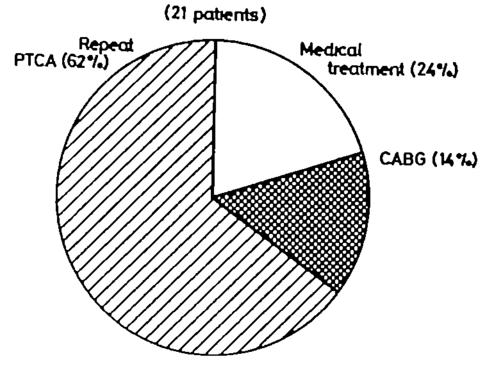

Fig 3 *Treatment of restenosis. PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.*

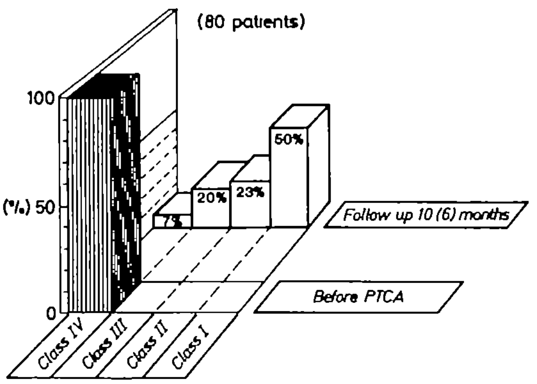

Fig 4 *Clinical follow up of patients after the last successful angioplasty procedure. PTCA, percutaneous transluminal coronary angioplasty.*

dilated vessels) from 54 (15) to 14 (10) mm Hg. Of 31 patients with multivessel disease, 15 had a successful complete revascularisation and in 13 angioplasty of the ischaemia associated lesions was successful. Acute myocardial infarction was a complication in four patients: two of them had emergency coronary bypass grafting. There were five additional failures caused by our inability to cross the coronary lesion, which was a total chronic occlusion in four patients. All four patients had sustained an infarction with minimal hypokinesis in the region perfused by the occluded vessel and had a severe stenosis on other vessels, with visible collaterals in two patients.

Follow up coronary angiography was performed at a mean (SD) interval of 10 (6) months (range 2–23 months) in 57 (71%) patients: it showed recurrence of stenosis in 21 (37%). Recurrence was recorded in 17 (35%) of 48 patients who had angioplasty of a single vessel and in 4 (44%) of nine patients who had multivessel angioplasty (NS). Repeat angioplasty (fig 3) was performed in 13 patients and it was successful in 12; one patient needed emergency coronary surgery because acute coronary occlusion occurred as a complication of the procedure. Three patients underwent elective coronary bypass grafting for the treatment of restenosis.

A clinical follow up was available for all patients with initially successful angioplasty at a mean interval of 10 (6) months after the last successful dilatation procedure. There were no deaths. One patient had sustained an acute myocardial infarction unrelated to the dilated vessel. Seventy four (93%) patients had improved by at least one New York Heart Association class for angina and 41 (50%) were symptom free (fig 4). At follow up 10 (80%) of 13 patients with multivessel disease and successful angioplasty of only the ischaemia related lesions were symptom free or had only mild angina. A stress test was performed in 52 patients as a part of the follow up evaluation at a mean interval of 12 (5) months (range 4–20 months) from the last coronary angioplasty procedure. Forty patients (77%) had neither signs nor symptoms of myocardial ischaemia at a mean workload of 117 (39) W (range 25–200 W) and a mean (SD) double product (blood pressure × heart rate) of 28 000 (6300) mm Hg/min. Twelve patients (23%) had angina or signs of myocardial ischaemia or both at a mean workload of 104 (35) W (range 50–175 W) and a mean double product of 25 000 (5500) mm Hg/min.

Discussion

The primary success rate in most reports of coronary angioplasty for unstable angina ranges from 61% in earlier studies[8] to 93% in more recent series when steerable systems were used.[9] Acute complications were reported in seven to 12%.[9–11] Our success rate (90%) and complication rate (5%) compare favourably with these reports and to some extent may reflect the inclusion in our series of patients with less severe coronary lesions. Coronary angiography was performed at follow up in 71% of our patients after a successful angioplasty. The patients in our series who declined follow up coronary angiography were usually symptom free. In 37% of our patients recurrence of stenosis was seen at angiography. This rate is higher than in other reports in which restenosis rates for patients with unstable angina ranged from 24%[7] to 32%.[11]

All our patients in whom angioplasty was successful had an immediate and considerable improvement in anginal symptoms. One patient sustained a myocardial infarction on a non-dilated vessel during the follow up period. Others have reported a similarly low frequency of infarction after a successful angioplasty for unstable angina.[9,11] A definite symptomatic improvement was apparent 10 (6) months after the last successful dilatation procedure in about two thirds of our patients, and one half of them were symptom free and with no sign of myocardial ischaemia on a stress test. Long term clinical improvement also persisted in the subset of patients with incomplete myocardial revascularisation—80% of them were either symptom free or had only mild angina. This accords with other reports of incomplete myocardial revascularisation by coronary angioplasty in patients with unstable angina.[10,12] Our data support observations that coronary angioplasty can be performed at an acceptable risk in selected patients with unstable angina. Immediate symptomatic improvement was achieved after a successful angioplasty of the angina related lesions and also in patients in whom myocardial revascularisation was incomplete. Long term improvement of angina was achieved in most patients; in some this required repeated coronary angioplasty.

References

1 Mulcahy R, Daly L, Graham I, *et al.* Unstable angina: natural history and determinants of prognosis. *Am J Cardiol* 1981;**48**:525–31.

2 Unstable angina pectoris: National cooperative study group to compare surgical and medical therapy. II. In-hospital experience and initial follow-up results in patients with one-, two-, and three-vessel disease. *Am J Cardiol* 1978,**42**:839–48.

3 Hultgren HN, Shettigar R, Miller DC. Medical versus surgical treatment of unstable angina. *Am J Cardiol* 1982;**50**:663–70.

4 Gerstenblith G, Ouyang P, Achuff S, *et al.* Nifedipine in unstable angina: a double-blind, randomized trial. *N Engl J Med* 1982;**306** 885–9

5 Gottlieb S, Weisfeldt M, Ouyang P, Mellitis D, Gerstenblith G. Silent ischaemia as a marker for early unfavourable outcomes in patients with unstable angina *N Engl J Med* 1986;**314**:1214–9.

6 Williams D, Riley R, Singh A, Gewirtz H, Most A. Evaluation of the role of coronary angioplasty in patients with unstable angina pectoris *Am Heart J* 1981;**102**:1–9.

7 Meyer J, Schmitz HJ, Kiesslich T, *et al* Percutaneous transluminal coronary angioplasty in patients with stable and unstable angina pectoris: analysis of early and late results. *Am Heart J* 1983;**106**:973–80.

8 Faxon D, Detre K, McCabe C, *et al.* Role of percutaneous transluminal coronary angioplasty in the treatment of unstable angina. Report from the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty and Coronary Artery Surgery Study registries. *Am J Cardiol* 1983;**53**:131C–5C.

9 De Feyter P, Serruys P, van den Brand M, *et al.* Emergency coronary angioplasty in refractory unstable angina. *N Engl J Med* 1985;**313**:342–6.

10 De Feyter P, Serruys P, Arnold A, *et al.* Coronary angioplasty of the unstable angina related vessel in patients with multivessel disease. *Eur Heart J* 1986;**7**:460–7.

11 Quigley PJ, Erwin J, Maurer BJ, Walsh MJ, Gearty GF. Percutaneous transluminal coronary angioplasty in unstable angina: comparison with stable angina. *Br Heart J* 1966;**55**:227–30.

12 Wohlgelehrnter D, Cleman M, Highman HA, Zaret BL. Percutaneous transluminal coronary angioplasty of the "culprit lesion" for management of unstable angina pectoris in patients with multivessel coronary artery disease. *Am J Cardiol* 1986;**58**:460–4.

13 Meier B, Rutishauser W. Transluminal coronary angioplasty—state of the art 1984. *Acta Med Scand* 1985;**70** (suppl):142–6.

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Sudden coronary death in Glasgow: the severity and distribution of chronic coronary atherosclerotic stenoses

M A EL FAWAL,* G A BERG,† D J WHEATLEY,† W A HARLAND*

*From the *Department of Forensic Medicine and Science, University of Glasgow and the †University Department of Cardiac Surgery, Royal Infirmary, Glasgow*

SUMMARY A detailed analysis of the extent of coronary artery atherosclerosis was made in 92 white subjects (66 men and 26 women) who died suddenly from ischaemic heart disease. Stenoses resulting in loss of $\geqslant 75\%$ of luminal cross sectional area (significant stenosis) were found in 90 subjects and these were more extensive in the proximal coronary tree than in the distal. Thirty nine per cent had triple vessel disease, 37% had double vessel disease, and 23% had single vessel disease. In addition one man had an isolated significant stenosis affecting the left main coronary artery. The frequency of significant stenoses in the left main coronary artery was greater in men than in women. The arteries that were least affected were the distal branches of the right coronary artery. A notable feature was the widespread nature of the coronary atherosclerosis: only 26 of the total of 1840 segments of coronary artery examined in the 92 victims could be described as having a normal intima ($\leqslant 10\%$ loss of the area within the internal elastic lamina).

The severity and the extent of advanced coronary atherosclerosis are recognised as important prognostic determinants in ischaemic heart disease, even when there are wide differences in age, race, geographical location, or other variables.[1–3] Data relating coronary artery disease to clinical manifestations and risk factors are largely based on an assessment of left ventricular function and the extent and degree of coronary atherosclerosis. Therefore, accurate evaluation of the severity and extent of coronary atherosclerotic lesions is important to clinical cardiologists, epidemiologists, and pathologists investigating the disease.

We examined the extent, severity, and location of coronary atherosclerotic lesions in 130 cases of sudden death. The degree of stenosis was accurately estimated with a quantitative microscope to record the loss of luminal cross sectional area of the whole epicardial tree after it had been divided into histological blocks taken at 3 mm intervals. Part of this study of sudden coronary death in Glasgow has already been reported.[4]

Patients and methods

We studied 130 white subjects under the age of 70 years (91 men and 39 women) who were submitted to medicolegal postmortem examination.

The coronary arteries were examined microscopically after postmortem angiography had been performed to determine the extent of coronary artery disease and the anatomy of the coronary arterial tree. The coronary arteries were dissected free from the heart, decalcified, and examined histologically. Blocks were taken at every 3 mm of the arteries and labelled according to a standard code (fig 1).[5] Each histological section was measured with a quantitative microscope attached to a microcomputer. The degree of stenosis was estimated by calculating the area representing the original lumen enclosed by the internal elastic lamina and the area of the residual lumen. The stenosis was expressed as a percentage loss of cross sectional area. The extent of athero-

Requests for reprints to Professor D J Wheatley, Department of Cardiac Surgery, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER.

Professor W A Harland died on 9 January 1985.

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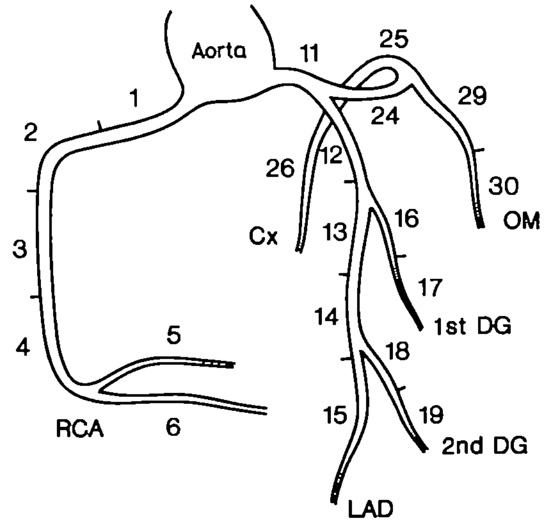

Fig 1 *Division of coronary tree into segments. Right coronary artery (RCA), segments 1–6; left main coronary artery, segment 11, left anterior descending artery (LAD), segments 12–15; first and second diagonal branches (1st DG and 2nd DG), segments 16 and 17 and 18 and 19 respectively; circumflex artery (Cx), segments 24–26; obtuse marginal artery (OM), segments 29 and 30.*

sclerotic narrowing in each segment of the coronary tree was measured and recorded as a percentage loss of luminal cross sectional area; those with stenoses $\geqslant 75\%$ were considered to be "significantly" stenosed. Results are given both for the total number of significant stenoses in each segment and for the distance along the arteries to the segment with the first significant stenosis. Left main coronary artery disease, as well as single, double, or triple vessel disease, was noted. Subjects in whom there were limited areas of narrowing of one or two segments of the coronary tree with the remaining arteries relatively free of disease were noted. The positions of normal segments of artery (arbitrarily defined as loss of luminal cross sectional area $\leqslant 10\%$) were noted.

Results

QUANTITATIVE ASSESSMENT OF SIGNIFICANT STENOSES

In 30 of the 130 subjects studied death was not caused by ischaemic heart disease. In eight subjects there was no identifiable cause of sudden death and, although coronary artery disease was present, there was no stenosis $\geqslant 75\%$ and no acute coronary event. In these cases the cause of death was in doubt. The remaining 92 subjects showed evidence of severe atherosclerosis or acute coronary events with no other identifiable cause of sudden death. Significant stenoses (that is $\geqslant 75\%$ loss of luminal cross sectional area) were found in 90 of the 92 cases of sudden ischaemic coronary death. When we compared the extent of stenoses in different parts of the coronary tree we found that certain segments showed a higher total number of significant stenoses than others (fig 2). The second and third 2 cm segments of the right coronary artery, the third and fourth 1·5 cm segments of the anterior descending coronary artery, and the 2 cm segment of the circumflex artery distal to its obtuse marginal branch had the highest number of significant stenoses.

LOCATION OF SIGNIFICANT STENOSES

Thirty five cases (39%) had triple vessel disease. Twenty five of these showed stenoses of $\geqslant 80\%$ in the three vessels, and in four cases the stenosis in each of the three vessels was $\geqslant 90\%$. Thirty three subjects (37%) had significant double vessel disease—four with an isolated stenosis in each affected vessel. Twenty one subjects (23%) had single vessel disease—five with one isolated stenosis and five having two discrete stenoses. One subject had a significant high grade stenosis in his left main coronary artery only.

The total number of significant lesions (fig 2) was greater in the proximal coronary tree than in the distal (312 and 197 stenoses respectively ($p < 0.01$)).

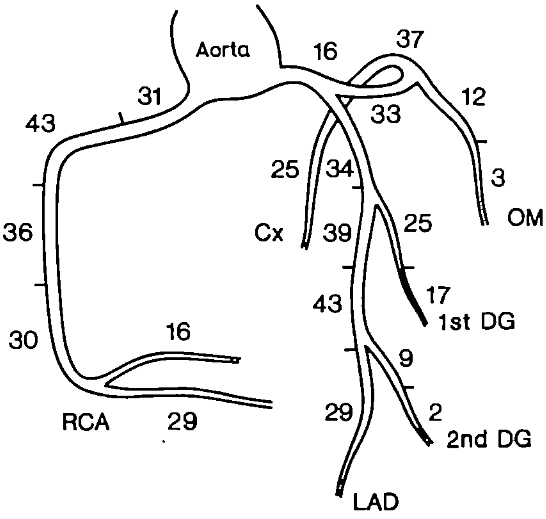

Fig 2 *Total number of significant stenoses in each segment of the coronary tree in 92 subjects (configuration as fig 1). RCA, right coronary artery; LAD, left anterior descending artery; 1st DG, first diagonal branch of LAD; 2nd DG, second diagonal branch of LAD, Cx, circumflex artery; OM, obtuse marginal artery*

Proximal segments for the purpose of this study were defined as the ten segments 1, 2, 3, 11, 12, 13, 14, 16, 24, and 29, and the ten distal segments were defined as 4, 5, 6, 15, 17, 18, 19, 25, 26, and 30 (fig 1). The increased severity of proximal disease was reflected in all three major coronary arteries. In 17 of the 92 cases, however, the distal parts of one or more of the main branches were more severely narrowed than the proximal parts. Twelve of these 17 cases had single distal lesions (that is one distal lesion in one of the major branches, with the rest of the vessels being relatively disease free). Four subjects had two vessels with distal lesions and one had three vessels with distal lesions.

The most frequent location for the first significant lesion encountered (that is the most proximal) along the coronary tree was the first segment of all three main branches (fig 3).

DISEASE OF THE LEFT MAIN CORONARY ARTERY

The total number of significant lesions in the left main coronary artery was significantly greater in men than women (fig 4 ($p < 0.02$)). There was no difference in the frequency of disease between those

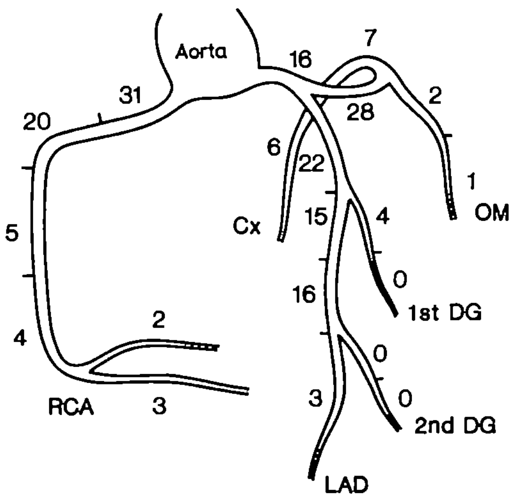

Fig 3 *Location of the most proximal significant stenosis in 92 subjects. RCA, right coronary artery; LAD, left anterior descending artery; 1st DG, first diagonal branch of LAD; 2nd DG, second diagonal branch of LAD; Cx, circumflex artery; OM, obtuse marginal artery.*

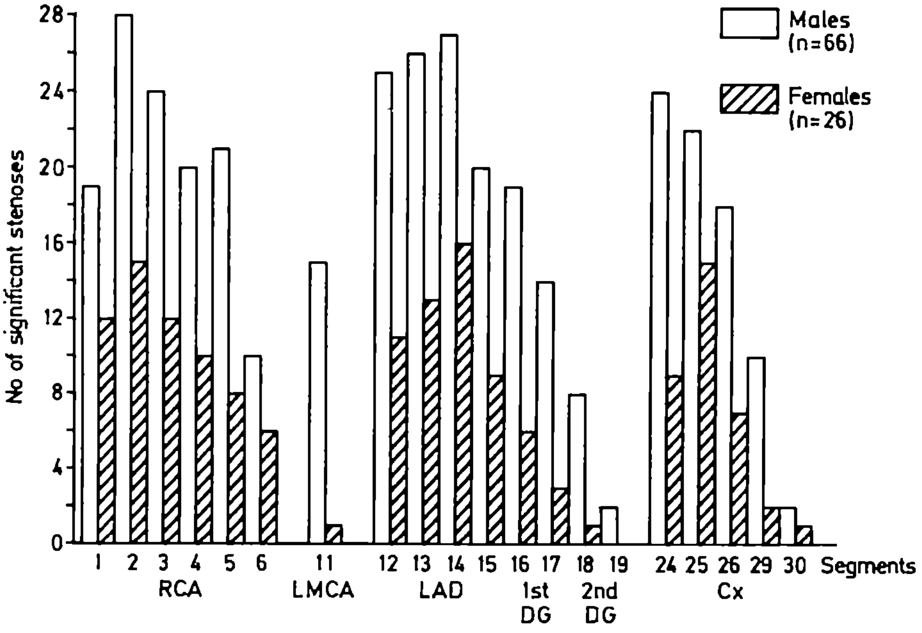

Fig 4 *Histogram of the numbers of significant stenoses in each segment for men and women. Numbers indicate segments as shown in fig 1. RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery; 1st DG, first diagonal branch of LAD; 2nd DG, second diagonal branch of LAD; Cx, circumflex artery.*

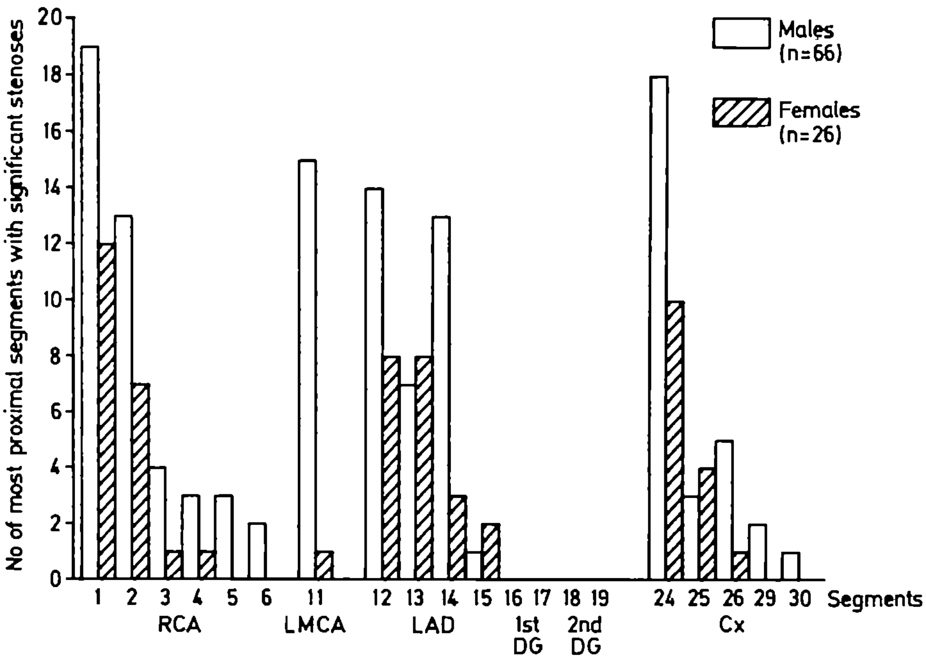

Fig 5 *Histogram of the number of the most proximal segments with significant stenoses in men and women. Numbers indicate segments as shown in fig 1. RCA, right coronary artery; LMCA, left main coronary artery, LAD, left anterior descending artery; 1st DG, first diagonal branch of LAD; 2nd DG, second diagonal branch of LAD; Cx, circumflex artery.*

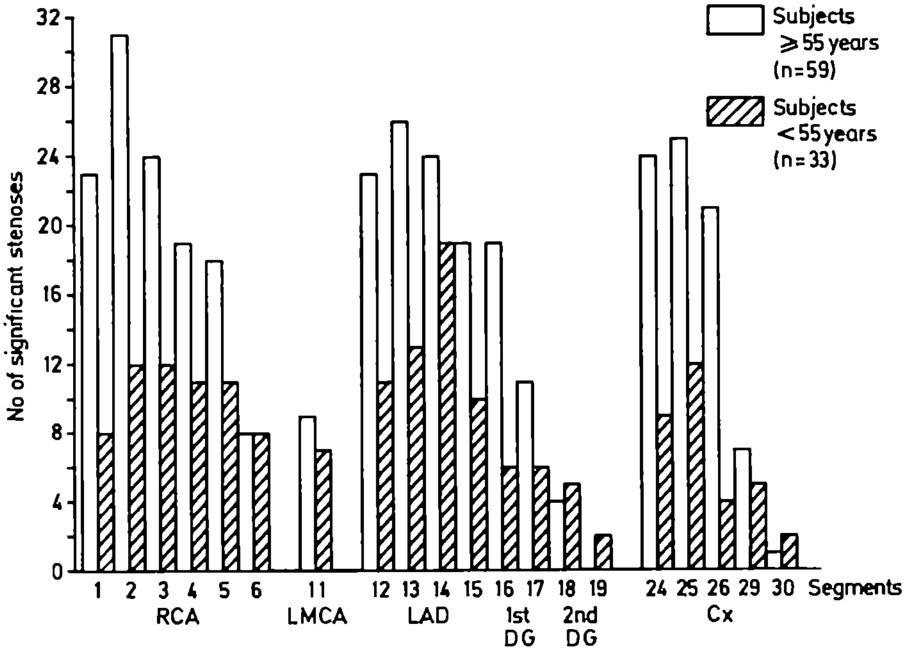

Fig 6 *Histogram of the numbers of significant stenoses in each segment for groups aged less than 55 years and more than 55 years. Numbers indicate segments as shown in fig 1. RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery; 1st DG, first diagonal branch of LAD; 2nd DG, second diagonal branch of LAD; Cx, circumflex artery.*

aged ≥ 55 and those aged <55. Isolated severe stenosis of the left main coronary artery occurred in only one case and there were no stenoses $>90\%$.

SEX AND AGE DISTRIBUTION

There was no difference between the total number of significant lesions (or the distance to the first significant stenosis) for men and women (fig 5). Similarly, there was no difference for those aged <55 years and those aged ≥ 55 years (fig 6).

NORMAL SEGMENTS

Segments with minimal atheroma (loss of cross sectional area $<25\%$) (fig 7) were more common in the distal coronary tree than in the proximal (136 compared with 50 segments respectively $(p < 0{\cdot}01)$). There were more normal segments in the right coronary artery than in the anterior descending or circumflex arteries. Only 26 segments had stenoses causing $<10\%$ loss of cross sectional area.

OLD LESIONS

Old lesions, represented by recanalisation, were found in 27 subjects; 24 of them had additional recent coronary lesions. Figure 8 shows the distribution of these old lesions, which were more common in the distal or smaller vessels. No old lesions were found in the proximal anterior descending artery, but more old lesions than acute lesions were found in the diagonal branches of this vessel.

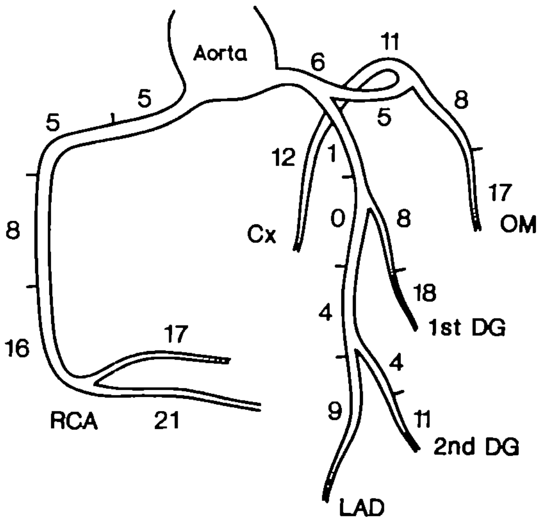

Fig 7 *Location of segments with loss of cross sectional area $<25\%$. Results from 92 subjects.*

DEATHS FROM CAUSES OTHER THAN ISCHAEMIC HEART DISEASE

Four of the 30 victims of sudden death with a cause other than ischaemic heart disease had significant stenoses. The range of loss of luminal cross sectional area was 7%–92% and the mean maximum loss of luminal area was 41·5%. Normal segments (loss of

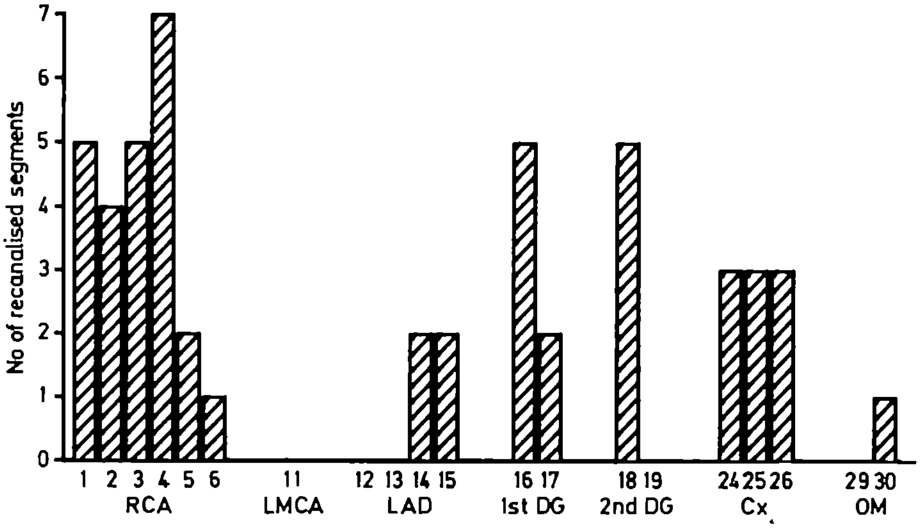

Fig 8 *Distribution of recanalised segments of coronary artery in 27 cases (numbers indicate segments as shown in fig 1). RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending artery; 1st DG, first diagonal branch of LAD; 2nd DG, second diagonal branch of LAD; Cx, circumflex artery; OM, obtuse marginal artery.*

luminal cross sectional area of < 10%) occurred in 56 out of the 600 segments of coronary arteries examined in these 30 subjects.

Discussion

It is well recognised that there are considerable age, sex, racial, and geographic variations in the prevalence of atherosclerosis.[4 6] A necropsy is not always performed on every patient with ischaemic heart disease who dies suddenly. For this reason the composition of groups of cases of sudden coronary death can be highly variable.

The most important measurement in the coronary tree of patients with coronary artery disease is the degree of stenosis.[7] The degree of coronary narrowing can be estimated with considerable precision[8]; however, an accurate evaluation of atherosclerotic lesions is only possible at necropsy. Techniques for the evaluation of the amount of coronary artery stenosis vary. In practice, pathologists have tended to use individual methods that render comparison rather difficult. Tracing the circumference of the residual lumen and the internal elastic lamina with a quantitative microscope is an accurate technique that can be reproduced in different populations.

A further difficulty arises in defining what is meant by a "severe" or "significant" stenosis, particularly in the context of sudden death. Many consider a stenosis producing 75% loss of the luminal cross sectional area as a significant factor in sudden coronary death.[9 10] The problem is further complicated by the question of whether the state of the arterial lumen at necropsy is a true index of the calibre during life. It is possible that factors such as artefacts produced by postmortem contraction and fixation may affect lumen size and shape. It has been suggested that when an artery is fixed under pressure similar to normal arterial blood pressure, raised plaques tend to recede into small concavities in the media.[11]

In this study the coronary tree was examined angiographically at necropsy to help in determining the cause of death and to localise areas of interest for sectioning. In our experience changing the injection pressure did not materially alter the degree of existing stenosis, provided that adequate filling of distal epicardial vessels was achieved. On the other hand, failure to fill the arteries completely with injection medium can lead to the collapse of the histological preparations and the eventual overestimation of the degree of narrowing by planimetry.

This study shows that in the majority of cases of sudden coronary death the proximal segments of the main branches of the coronary tree are more severely affected than the distal segments. Such findings may accord with the suggested importance of the role of haemodynamic factors in plaque formation.

Atherosclerotic lesions were widespread in all the subjects in this study (even those not dying of ischaemic heart disease). There was disease in most segments examined. Only 26 of the 1840 segments examined from the 92 subjects in whom death from ischaemic heart disease was confirmed had a loss of coronary artery cross sectional area $\leqslant 10\%$. Only 56 of the 600 segments from the 30 subjects who died of causes other than ischaemic heart disease had a loss of cross sectional area $\leqslant 10\%$. Many of these histologically diseased segments had an angiographically normal appearance.

This study has shown that a considerable proportion of subjects with ischaemic heart disease who die suddenly have only single vessel disease and this group, particularly, might be considered to have a good prognosis if seen in life. All cases warrant full resuscitative efforts. This study and our previous one[4] provide further evidence that the same pathological processes underlie sudden death from ischaemic heart disease and unstable angina or evolving myocardial infarction.[12]

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References

1 Guzman MA, McMahan CA, McGill HC, *et al.* Selected methodologic aspects of the International Atherosclerosis Project. *Lab Invest* 1968,**18**:479–97.

2 Deupree RH, Fields RI, McMahan CA, Strong JP. Atherosclerotic lesions and coronary heart disease. Key relationships in necropsied cases. *Lab Invest* 1973;**28**:252–62.

3 Takaro T and the participants in the VA Co-operative Study of surgery for coronary arterial occlusive disease. Results of a randomised study of medical and surgical management of angina pectoris. *World J Surg* 1978;**2**:797–809.

4 El Fawal MA, Berg GA, Wheatley DJ, Harland WA. Sudden coronary death in Glasgow: nature and frequency of acute coronary lesions *Br Heart J* 1987,**57**.329–35

5 Brandt PW, Partridge JB, Wattie WJ. Coronary arteriography: method of presentation of the arteriogram report and a scoring system. *Clin Radiol* 1977; **28**.361–5.

6 Sacks MI. Aortic and coronary atherosclerosis in the three racial groups in Cape Town. *Circulation* 1960;**22**:96–109.

7 Crawford T. *Pathology of ischaemic heart disease.* London: Butterworth, 1977.26.

8 Wijns W, Surruys PW, Reiber JH, *et al.* Quantitative angiography of the left anterior descending coronary

artery: correlations with pressure gradient and results of exercise thallium scintigraphy. *Circulation* 1985;71:273–9.

9 Davies MJ, Thomas A. Thrombosis and acute coronary artery lesions in sudden cardiac ischaemic death. *N Engl J Med* 1984;310·1137–40.

10 Warnes CA, Roberts WC. Sudden coronary death: comparison of patients with, to those without, coronary thrombus at necropsy. *Am J Cardiol* 1984, 54:1206–11.

11 Crawford T, Levene CI. Incorporation of fibrin in the aortic intima. *J Path Bact* 1952;64:523–8.

12 Falk E. Unstable angina with fatal outcome: dynamic coronary thrombosis leading to infarction and/or sudden death. Autopsy evidence of recurrent mural thrombosis with peripheral embolisation culminating in total vascular occlusion. *Circulation* 1985;71: 699–708.

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Incidence, risk, and outcome of reintervention after aortocoronary bypass surgery

KARIN LAIRD-MEETER, RON VAN DOMBURG, MARCEL J B M VAN DEN BRAND, JACOBUS LUBSEN, EGBERT BOS, PAUL G HUGENHOLTZ

From the Thorax Center, University Hospital Dijkzigt, Erasmus University Rotterdam, The Netherlands

SUMMARY Reintervention was required in 123 (12%) individuals during a follow up (mean 7·5 years, range 5–14·5) of 1041 patients with consecutive, isolated, first aortocoronary bypass operations. In 89 patients the intervention was a repeat bypass operation, in 24 it was angioplasty, and 10 had both. Procedure related mortality was significantly higher at reintervention (5·6%) than at the primary operation (1·2%). Survival probability after a single bypass procedure was 90% at six years and 82(3)% at nine years. Corresponding figures six and nine years after reintervention were 89(6)% and 87(7)% respectively. Stepwise multivariate analysis showed that survival was significantly correlated with left ventricular function (rate ratio 1·82) and with extent of vascular disease (rate ratio 1·80) but not with reintervention (rate ratio 1·45). Symptomatic improvement occurred in 89% of the survivors with or without reintervention.

Repeat procedures are often necessary after coronary artery bypass grafting but they appear to provide appreciable relief of symptoms without reducing any long term improvement in survival brought about by the original operation.

Coronary artery bypass grafting has been used successfully to treat angina pectoris since 1968.[1] It is now clear that it is not a definitive treatment. Most patients experience an improvement in symptoms but this relief decreases with time.[2–4] Both Campeau *et al* and Lytle *et al* reported an accelerated loss of graft patency after five years or more.[5 6] Moreover, atherosclerosis is a progressive disease. As a result, reoperations after coronary artery bypass grafting are increasingly performed[7–9] and angioplasty has been introduced to improve myocardial blood flow either by dilatation of a stenosed bypass graft or by dilatation of an unbypassed narrowed native artery.[10 11]

To assess the frequency of re-revascularisation achieved by re-grafting or angioplasty, we studied a group of consecutive patients who had isolated coronary artery bypass grafting before July 1980. We looked especially at symptomatic improvement after both these procedures, the timing, the procedure related risk(s), and the probability of long term survival with and without reintervention.

Patients and methods

PATIENT SELECTION AND CHARACTERISTICS

We studied the 1041 patients who had undergone isolated aortocoronary bypass surgery at our hospital between 1971 and July 1980. The indication for the original operation was angina pectoris unrelieved by the pharmacological treatment that was considered optimal at that time. Table 1 shows the clinical characteristics of these patients. Follow up data on this series of patients have been reported elsewhere.[12 13] All reinterventions performed in this group of patients up to July 1985 are included. Before 1982 a reintervention meant a coronary artery bypass re-grafting, whereas after 1982 an angioplasty procedure was performed in selected cases. If more than one reintervention had been performed, the first was used as the data collection point.

CATHETERISATION DATA

A selective coronary angiogram was obtained in all patients before a procedure. A vessel was considered

Requests for reprints to Dr Karin Laird-Meeter, Thorax Center, University Hospital Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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Table 1 *Clinical characteristics of patients at primary operation (n = 1041) and at the primary and repeat procedure in those who had reintervention (n = 123)*

Data	*Entire cohort at primary operation*		*Patients with reintervention*			
			*At 1st operation**		*At reintervention*	
Men	915	(88%)	114	(93%)	114	(93%)
Women	126	(12%)	9	(7%)	9	(7%)
Age						
≤ 50	360	(35%)	63	(51%)	33	(27%)
51–60	489	(47%)	53	(43%)	66	(54%)
>60	192	(18%)	7	(6%)	24	(19%)
Mean	53 4†		49·7†		54 2	
Diseased:						
1 vessel	192	(19%)	25	(20%)	11	(9%)
2 vessels	320	(31%)	41	(34%)	19	(15%)
3 vessels	444	(42%)	47§	(38%)	81§	(66%)
Left main	85	(8%)	10§	(8%)	12§	(10%)
Ejection fraction:						
$\geq 0{\cdot}55$	600‡	(57%)	84‡	(68%)	78	(63%)
0 31–0 55	248‡	(24%)	16‡	(13%)	31	(25%)
≤ 0 30	27	(3%)	3	(3%)	3	(3%)
Unknown	166	(16%)	20	(16%)	11	(9%)
Validity						
NYHA class I	0	(0%)	—	(0%)	—	(0%)
II	Subdivision		46	(37%)	1	(1%)
III			66	(54%)	69	(56%)
IV	unknown		11	(9%)	53	(43%)

*At primary operation of group with subsequent reintervention; †p < 0 001, entire cohort *vs* reintervention group, ‡p < 0 005, entire cohort *vs* reintervention group; §p < 0 001, reintervention group at primary operation *vs* at reintervention.

to be diseased when a luminal narrowing of $>50\%$ was seen in more than one projection. Coronary disease was classified as one, two, three, or left main vessel disease. At repeat catheterisation the bypass graft was injected selectively where possible. If the bypass graft could not be opacified and if the graft was found to be closed at operation or if the graft could be opacified but showed a narrowing of $>90\%$ the graft was regarded as a failure. We diagnosed progression of atherosclerosis if at a later catheterisation a major artery showed an increase in luminal narrowing from a previously normal or $<50\%$ narrowed lumen to narrowing of $\geq 50\%$ or from $\geq 50\%$ narrowing to a total or subtotal occlusion.

If a severely narrowed major vessel could not be bypassed at operation revascularisation was regarded as inadequate. A surgical procedure was considered to have been faulty if the bypass graft was either incorrectly placed on the intended artery or was placed on the wrong artery.

Left ventricular angiography was performed in all patients. If the angiogram was technically satisfactory an ejection fraction was calculated. Ejection fractions of $\geq 0{\cdot}55$ were considered to be normal; those of $\leq 0{\cdot}30$ were called poor and those that were $> 0{\cdot}30$ but $< 0{\cdot}55$ were described as moderately decreased.

ANGIOPLASTY

In 1982 angioplasty procedures were first used at our hospital on patients with coronary artery bypass grafts. The technique of Gruntzig *et al*[14] was used with a steerable balloon catheter inserted via the femoral route. Of the patients in this study group 14 underwent dilatation of a narrowed or occluded bypass graft, 19 had dilatation of one or more native coronary arteries, and one had dilatation of a bypass graft and a native vessel in the same session. Indications for the procedure were: symptoms of myocardial ischaemia in a patient in whom angiography showed that dilatation was feasible or a distal coronary vascular bed with poor run off which precluded surgical treatment (six cases). In the latter case only the ischaemia related vessel was dilated as an emergency measure[15] because no alternative method of treatment could be used.

A dilatation was regarded as successful when it resulted in clinical relief of the symptoms of ischaemia, when the residual stenosis was $<50\%$ of the luminal diameter and the mean pressure gradient across the stenosis, normalised for aortic pressure, had decreased to 0·30 of the original. The procedure was judged to have been successful in 25 (74%) patients. In one (3%) patient an emergency operation was necessary; in five (15%) others coronary artery bypass grafting followed one week to seven months later.

SURGICAL TECHNIQUE

All patients in the study were originally operated on by the same team. In 1977 sequential grafting was introduced[16] and in 1983 topical cardiac cooling was replaced by cold cardioplegic arrest with St

Table 2 *Mean number of distal anastomoses per patient made at the primary operation in the groups without and with subsequent intervention*

	No reintervention		*Reintervention later*	
Vessels diseased at primary operation	*Number of patients*	*Anastomoses per patient*	*Number of patients*	*Anastomoses per patient*
1 vessel	167	1·4	25	1·4
2 vessels	279	2·3	41	2·3
3 vessels	397	3·4	47	3·3
Left main	75	3·4	10	3·0
Total	918	2·6	123	2·5

Thomas's Hospital solution for myocardial preservation.[17]

In all instances complete revascularisation was attempted. At the original surgical procedure a mean of 2·6 distal anastomoses were made (range 1–7). At the repeat operation vascularisation was improved in all but two patients. One of these was given an aortic valve prosthesis and the other underwent aneurysmectomy and mitral valve replacement.

FOLLOW UP

Follow up data were determined through the civil registry: 99% of the 1041 patients could be traced. Deaths from all causes were included in the analysis. A complete follow up of the group with a reintervention was possible. After a reintervention the treating physician or the principal investigator assessed the occurrence of symptoms in each patient. Angina pectoris was regarded as present after a procedure if the subject experienced chest pain with the same characteristics as before the operation. The New York Heart Association classification was used.

STATISTICAL ANALYSIS

Where appropriate the χ^2 contingency test was used. The probability of survival was calculated by the Kaplan and Meier method.[18] To determine whether a reintervention constituted a separate risk in long term survival, data were analysed by a stepwise nonlinear algorithm of the Cox proportional hazards model.[19 20] For those patients who did not have a second procedure, we entered the appropriate data collected at the time of the original operation. Otherwise, the data were collected at the time of reintervention.

Results

Within follow up (minimum five years, mean 7·5 years) 123 (12%) patients of the study population had a repeat intervention. The symptoms and vascular lesions shown by these patients at the original coronary artery bypass grafting were similar to those of the 918 who did not have a reintervention (table 1).

The patients with a reintervention were younger at the initial operation (49·7 years *vs* 53·4 years ($p < 0{\cdot}001$)) and their left ventricular function, as expressed by ejection fraction, was better (table 1). The ejection fraction was normal in 84 (68%) of the 123 patients who needed a reintervention; it was moderately decreased in 16 (13%). In the 918 patients who did not have a reintervention at a later date 56% had a normal ejection fraction and 25% had a moderately decreased one ($p = 0{\cdot}002$).

The number of grafts implanted did not differ greatly in the two groups. Table 2 shows that a mean of 2·5 distal anastomoses was made in the reintervention group compared with 2·6 in the group without subsequent reintervention.

No consistent data were available on established risk factors such as hyperlipidaemia and high blood pressure. Patients with these risk factors were treated appropriately.

CHANGES IN THE REINTERVENTION GROUP

Table 1 shows the characteristics of the 123 patients who needed a reintervention. There was a striking change in symptoms. Before the primary operation 46 (37%) patients were in class II; at the time of the reintervention only one patient was in this class. The number of patients with angina pectoris at rest despite maximal pharmacological treatment (class IV) had increased from 11 (9%) to 53 (43%).

Table 1 also shows that at primary operation slightly more than half the patients had one or two vessel disease (66 (54%) *vs* 57 (46%) with three vessel or left main disease). At reintervention this distribution had changed significantly to 30 (24%) and 93 (76%) respectively ($p < 0{\cdot}001$).

INTERVAL BETWEEN PROCEDURES

The interval between the initial coronary artery bypass grafting and reintervention ranged from 1·5 months to 12·5 years (mean 4·5 years). In the first postoperative year 23 patients (2·3% of the first year

Table 3 *Anatomical lesion at reintervention with time of occurrence of angina pectoris in months after the primary operation*

Findings	*No of patients*	*Angina pectoris after primary operation (months)* 0–6	6–12	>12	*Range (months)*
Graft failure alone	32 (26%)	22	5	5	21–36
Graft failure and progression in grafted artery	24 (20%)	11	1	12	28–149
Graft failure and progression in non-grafted arteries ± progression in grafted artery	42 (34%)	2	1	39	13–130
Progression in non-grafted artery	15 (12%)	—	—	15	14– 96
Technical shortcoming in first operation	5 (4%)	5	—	—	—
Aortic valve stenosis	5 (4%)	2	—	3	21– 36
Total	123	42	7	74	14–149

survivors) underwent a reoperation. Figure 1 shows the cumulative number of patients with a reintervention. The number of patients needing a reintervention (11 per year) remained constant up to the tenth postoperative year. Angioplasty was gradually introduced several years after the intake of patients in the study group had stopped.

ANATOMICAL LESION AT REINTERVENTION

At reintervention the predominant finding was graft failure in 98 (80%) of the 123 patients. There was pure graft failure without changes in the native coronary vessels in 32 (26%) patients. In 24 (20%) graft failure was noted with progression of vascular lesions in the grafted artery and in 42 (34%) we found graft failure and progression of atherosclerosis in a non-grafted artery with or without progression in the grafted vessel (table 3). All intended grafts were functioning correctly in only 17 (14%) of the 123 patients. Fifteen of these 17 patients had progression of lesions in the non-grafted arteries and in two an aortic valve stenosis had developed with mean gradients across the valve of 75 and 90 mm Hg,. Three other patients with aortic valve disease also had failing grafts at reoperation.

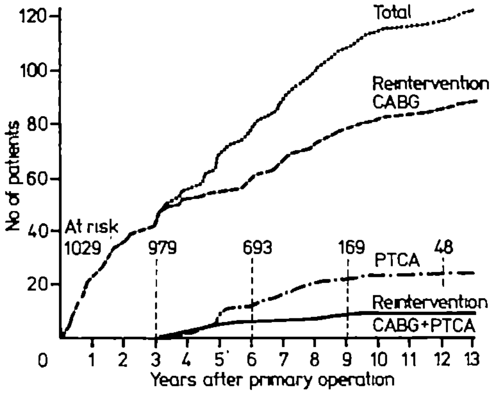

Fig 1 *Cumulative number of patients with a reintervention (re-grafting, angioplasty, or both) versus interval since the primary bypass operation. The increase is constant from the second to the 10th postoperative year despite the decreasing number of patients at risk. PTCA, percutaneous transluminal coronary angioplasty. CABG, repeat coronary artery bypass grafting.*

The failure rate of the grafts at a mean of 4·2 years after the initial operation in the patients needing a reintervention was 72% (226/312); the usual overall failure rate three years after operation at that time was 24%.[21]

PERIOPERATIVE MORTALITY

The 28 day operative mortality after the primary coronary artery bypass grafting procedure was 1·2% (12/1041). After a reintervention 6·5% (8/123) of the patients died. Some patients needed a second angioplasty or a surgical intervention after angioplasty. In total 142 procedures were performed (table 4), with a procedure related mortality of 5·6% (8/142). Mortality after reintervention was significantly higher than after the first coronary artery bypass grafting ($p < 0{\cdot}005$). Most cases of perioperative death were caused by an acute myocardial infarction during, shortly before, or shortly after the procedure.

LONG TERM SURVIVAL

Figure 2 shows the probability of survival for the

Table 4 *Mortality related to reoperation and angioplasty in 123 patients with previous bypass surgery*

Type of intervention	*No of procedures*	*Mortality*	
Surgical procedures			
Second operation	91	6	(6·6%)
Reoperation after unsuccessful angioplasty	8	—	—
Third operation	2	—	—
Total	101	6	(5·9%)
Angioplasty procedures:			
Angioplasty after first operation	32	2	(6·3%)
Angioplasty after second operation	2	—	—
Second angioplasty	5	—	—
Third angioplasty	2	—	—
Total	41	2	(4·9%)
Total reinterventions	142	8	(5·6%)

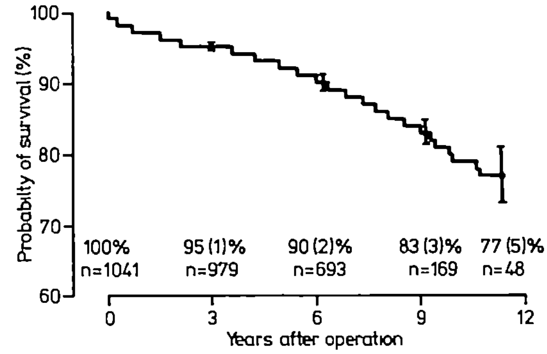

Fig 2 *Probability of survival in the total group plotted against time after surgery. The number of patients alive at the end of each year is shown. The vertical bars are the 95% confidence interval.*

entire group of 1041 patients after the primary coronary artery bypass grafting. Five years after operation survival was 92%, at six years it was 90(2)%, and at nine years it was 83(3)%. In those who had a reintervention the three year probability of survival was 98(2)%, at six years it was 96(3)%, and at nine years it was 91(6)%. After exclusion of the perioperative mortality associated with the primary operation the probability of survival in the patients who did not have a reintervention was slightly lower than that in the patients who did (96(2)%, 91(2)%, and 83(3)% at 3, 6, and 9 years respectively). Figure 4 shows the survival curve of the same patients starting at either the initial bypass operation or the first reintervention. The intervention related mortality is included. Thus the long term survival rate after a first revascularisation may be compared with that

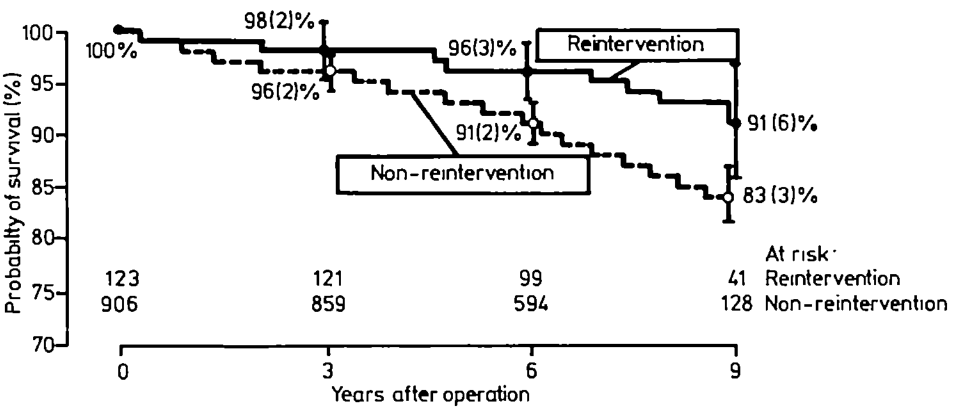

Fig 3 *Probability of survival for patients with and without a subsequent reintervention plotted against time after the initial operation. Operative mortality at original surgery is excluded. The number of patients alive at the end of each year is shown. The vertical bars are the 95% confidence interval.*

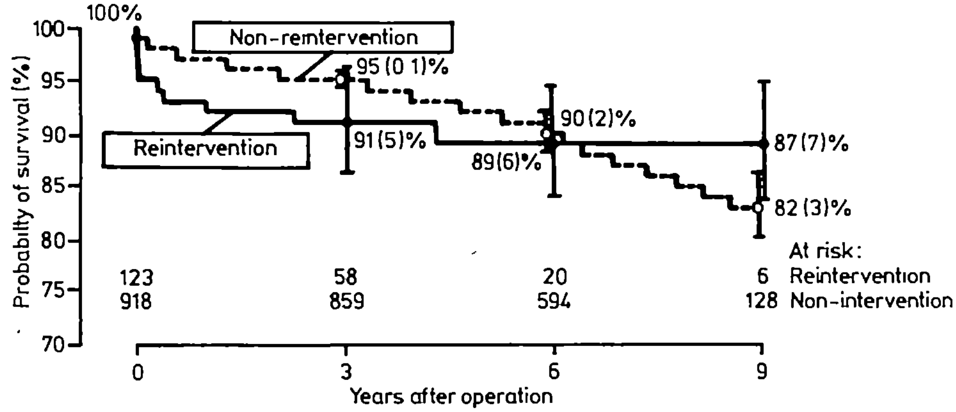

Fig 4 *Probability of survival after a first bypass operation and after a second procedure, plotted against time after either intervention. The number of patients in each group alive at the end of each year is shown. The vertical bars are the 95% confidence interval.*

Table 5 *Rate ratio from Cox's regression analysis of survival*

Factor	*Rate ratio*	*p value*
Age at operation:		
Continuous variable	1·02/yr	NS
Sex		
Men	Reference category	—
Women *vs* men	1·12	NS
Vascular disease:		
1 vessel disease	Reference category	—
2, 3, and LM *vs* 1 vessel disease	1·18	NS
3 and LM *vs* 1 vessel disease	1·80	0·01
Ejection fraction		
Normal	Reference category	—
Depressed *vs* normal	1·82	0·0007
Non-reintervention group	Reference category	—
Re-intervention *vs* non-reintervention	1·45	NS

LM, left main stem coronary artery disease.

after a re-revascularisation. The initially high procedure related mortality in the reintervention group gave a probability of survival to three years of 91(5)%; the corresponding result after a first grafting procedure was 95% (this figure takes account of the perioperative mortality). The probability of survival to six years was similar in the two groups: 89(6)% and 90(2)%. The likelihood of survival to nine years in the reintervention group was 87(7)%.

RELATIVE RISK OF REINTERVENTION

To discover whether reintervention poses a risk that is independent of other recognised risk factors such as preoperative vascular disease and reduced ejection fraction, we performed a stepwise multivariate analysis. For the reintervention group we entered data collected at the time of the procedure. For patients without a reintervention we used the data collected at the primary operation. The reintervention was entered as a separate item. The results of the analysis are expressed as rate ratios—that is the death rate (number of events per unit of person-time of follow up) in a particular category divided by the death rate in a reference category, given that other characteristics entered in the survival model are equal. Table 5 shows the rate ratio point estimates. The only statistically significant predictors of long term survival were the extent of vascular disease and the ejection fraction. The reintervention in itself did not carry an additional risk, all other factors being equal (the rate ratio of reintervention versus first revascularisation was 1·45, NS).

SYMPTOMS AT FOLLOW UP

Just before reintervention 122 (99%) patients were either in class III or IV of the New York Heart Association classification. At follow up, a mean of 2·9 years after the reintervention (range 0·1–12·6 years) none of the 107 survivors were in class IV, 14 (13%) were in class III, and 45 (42%) were in class II. Overall, 49% (52 of the 107 survivors) still had symptoms of angina, but 89% felt definitely improved. Three years after operation 42% of the patients with one grafting procedure had anginal complaints; in 15% the symptoms were mild and did not limit daily activity. Eighty nine per cent of the reintervention group reported that they felt better after the procedure. Thus the frequency of angina pectoris was not significantly different in the group that had a reintervention and those that had only a primary operation.

Discussion

It was reassuring to find that the probability of survival after a reintervention was not significantly different from that after the first coronary artery bypass grafting procedure. At first glance this seems to be inconsistent with the higher procedure related mortality at repeat intervention: 5·6% *vs* 1·2% for the first coronary artery bypass grafting. Loop *et al* from the Cleveland Clinic reported a higher perioperative mortality rate at reoperation too.[8] They reported that operative mortality decreased from 4·8% in the early years of the technique to 2% in 1981 and 1982; this is still higher than the usual mortality rate for a first coronary artery bypass grafting procedure (<1%). Forster *et al* compared operative mortality for repeat and initial coronary artery bypass grafting in the Coronary Artery Surgery Study registry. They reported that the risk was increased from 3·1% to 5·3% at reoperation.[22] Yet we and other investigators found that survival after reoperation compared well with that after first coronary artery bypass grafting. In Loop *et al*'s series, overall five year survival was 89% in their first 750 patients.[8] Reul *et al* reported a cumulative seven year survival of 82% in 168 patients who had a reoperation[23]; this is very similar to the survival rate of 84% at seven years that they reported for their entire revascularisation series of 13 049 cases.

We found a high survival rate in patients who required a reintervention in the course of their disease. Six years after a bypass procedure 96(3)% of patients who had a reintervention were alive and 91(2)% of those without a repeat procedure were alive.

Selection bias may well be responsible for this result. Patients who later required reintervention were younger at the initial surgery and had better left ventricular function at that time; however, symptoms and preoperative vascular disease were similar in the two groups. Selection bias (at entry patients who later had reoperation had different characteristics from those who did not) was found in the Coronary Artery Surgery Study too.[22] Moreover, to be selected for a repeat revascularisation patients must reach the hospital alive without other important disease.

Despite the higher initial mortality associated with the repeat procedure, long term survival was the same after a repeat revascularisation procedure as after initial coronary artery bypass grafting. Statistical testing in which the extent of vascular disease and left ventricular function were controlled for showed that intervention did not have an independent adverse influence on survival.

REASON FOR REINTERVENTION

Several factors may account for coronary artery bypass grafting being less successful than expected: faulty operative technique, early thrombotic obstruction of the grafts,[24 25] failure of the graft caused by fibrous intimal proliferation (generally occurring during the first postoperative year),[25] graft atherosclerosis several years after coronary artery bypass grafting,[26] and progression of the atherosclerotic disease in the native coronary vasculature.[5] All these factors were found in our series. One patient also had mitral valve insufficiency and five had aortic valve stenosis. These are unusual reasons for reintervention, but they were found during a follow up of consecutive patients.

Early graft failure with persistent angina was seen in 18% (22/123) of the patients who had reintervention. There was recurrence of pain after an angina free interval of up to three years caused by pure graft failure in 8% (10/123). Progression of obstruction but with patent grafts was seen in patients who had symptoms more than a year after operation. Late recurrence of symptoms was related to progression of atherosclerosis in native arteries as well as in grafts. Hence, the timing of the occurrence of symptoms did not indicate their underlying cause.

FREQUENCY OF REINTERVENTION

Soon after coronary artery bypass grafting became a routine operation it was realised that some patients would require reoperation, but what proportion was not known. Loop *et al* assume that 7% of today's patients will undergo a reoperation in the next 10 years.[8] Lawrie *et al* found a 9% reoperation rate during 10 years of follow up.[27] Others have reported reoperation rates as high as 33% in patients operated on between 1970 and 1975; this rate decreased, however, with more experience with these operations.[28] The reintervention rate of 12% in our study, during a mean follow up of 7·5 years, is disturbingly high. This may, in part, be related to the effect of the learning curve. Undoubtedly, fewer grafts were implanted in the early 1970s than at present. Some workers argue that the greater the number of grafts that are initially implanted in a patient the less likely is progressive atherosclerosis to develop in previously ungrafted arteries and to become an indication for reoperation.[8 29] In our study a similar number of grafts were inserted at the initial coronary artery bypass grafting in patients with and without a later intervention.

The high reintervention rate in our population might also have been the result of increased progression of atherosclerosis in the grafts and native arteries. The overall survival of the total group of 1041 patients, which compares favourably with other series, however, argues against this. Five year survival in our study (92(2)%) resembles five year survival after surgery reported by Myers *et al* in the Coronary Artery Surgery Study,[30] by Cosgrove *et al* at the Cleveland Clinic,[31] and by Varnauskas in the European Coronary Surgery Group[32] (90%, 93·2%, and 92·4% respectively). The 10 year survival of 79·3% in the Cleveland Clinic series[31] accords with our result (79 (4)%).

Lastly, the high reintervention rate might be inherent in the local referral process. The decision to use invasive treatment was not taken lightly—patients had severe symptoms before reintervention. Patients with unstable angina pectoris were referred by the cardiology service, whereas those with stable symptoms were referred directly to the surgical service. All patients entered the same register. This reintervention rate may more closely reflect the real position than a study based on referral to a distant centre for purely elective procedures. Moreover, our study included angioplasty procedures as reinterventions. The cumulative graph of patients requiring a reintervention over time (fig 1) shows a steady rise in the number of patients needing a reintervention, despite the decrease in the number of patients at risk. The cause for the reintervention is clearly a continuing vascular disorder, which progresses with time. This increase may correspond with the accelerated loss of graft patency years after coronary artery bypass grafting as described by Campeau *et al.*[26]

ANGIOPLASTY VERSUS CORONARY ARTERY BYPASS GRAFTING

The treatment results of coronary artery bypass grafting and angioplasty cannot be compared because only 34 patients had angioplasty. Twenty eight patients had the conventional indication for angioplasty—a localised lesion in a vessel without many collaterals—and in six the lesion was unsuitable for surgical intervention. It was the treatment of last resort for unstable angina unresponsive to intensive pharmacological treatment. In these patients the ischaemia related vessel was dilated as described by de Feyter *et al.*[15] Hartzler *et al* reported a success rate of 92% and a mortality of 5 6% in a series of 500 patients with multivessel disease[33]; our success rate was lower (74%), as was our mortality rate of 4·9%. Nevertheless, angioplasty is an alternative to coronary artery bypass grafting, both for dilatation of native vessels and grafted vessels.[10 11]

SUBJECTIVE CONDITION AT FOLLOW UP

Complete relief of anginal complaints is reportedly achieved less often after a reoperation than after a first coronary artery bypass grafting.[8 13] In the present study this was not the case. We found that 49% of the survivors had anginal symptoms after their reintervention; this resembles the results in patients three years after a single operation (42%). In a previous study of 53 patients with reoperations followed up for a mean of 3·5 years after the original operation we found that 68% of patients had angina.[13] It is possible that the recent improvement has been brought about by increased experience.

Loop *et al* found that 48% of patients had angina after reoperation whereas after a single operation only 25% had symptoms.[8] This last low percentage might be caused by the use of a different method as Campeau *et al*[3] found a recurrence rate of anginal complaints after a single operation that was similar to ours.

LIMITATIONS OF THE STUDY

Ours is not a prospective study nor did we perform serial cardiac catheterisation. Therefore, we do not know when atherosclerosis started in the bypass grafts. Moreover, data on risk factors, such as lipid spectrum and level of blood pressure were not recorded consistently at the start of the study. Thus it was not possible to correlate risk factors with the likelihood of subsequent reintervention.

It is not uncommon for patients with coronary bypass grafts to require a reintervention because of severe angina. We found, however, that with the current techniques the long term prognosis is good. When the extent of vascular disease and left ventricular function are taken into consideration the survival probability is as good as after a first bypass procedure, and there is a considerable improvement in symptoms after the procedure.

References

1 National Institutes of Health Consensus Development Statement. Coronary-artery bypass surgery. scientific and clinical aspects *N Engl J Med* 1981; 304:680–4.

2 Rahimtoola S. Coronary bypass surgery for chronic angina 1981 A perspective. *Circulation* 1982;65: 225–41.

3 Campeau L, Lespérance J, Hermann J, Corbara F, Grondin CM, Bourassa MG. Loss of improvement of angina between one and seven years after coronary bypass surgery *Circulation* 1979;60(suppl I)I:1–5

4 Cameron A, Kemp HG, Shimomura S, *et al.* Aorto coronary bypass surgery. A 7-year follow-up. *Circulation* 1979;60(suppl I)I.9–13.

5 Campeau L, Enjalbert M, Lespérance J, *et al* The relation of risk factors to the development of atherosclerosis in saphenous-vein bypass grafts and the progression of disease in the native circulation. *N Engl J Med* 1984;311:1329–32

6 Lytle BW, Loop FD, Cosgrove DM, Ratcliff NB, Easley K, Taylor PC. Long-term (5–12 years) serial studies of internal mammary artery and saphenous vein coronary bypass grafts. *J Thorac Cardiovasc Surg* 1985,89:248–58.

7 Schaff HV, Orszulak TA, Gersh BJ, *et al.* The morbidity and mortality of reoperation for coronary artery disease and analysis of late results with use of actuarial estimate of event free interval. *J Thorac Cardiovasc Surg* 1983;85 508–15

8 Loop FD, Lytle BW, Gill CC, Golding LAR, Cosgrove DM, Taylor PC Trends in selection and results of coronary artery reoperations. *Ann Thorac Surg* 1983;36 380–8.

9 Foster ED. Reoperation for coronary artery disease. *Circulation* 1985;72(suppl V)V:59–64.

10 Jones EL, Douglas JS, Gruntzig AR, *et al* Percutaneous saphenous vein angioplasty to avoid re-operative bypass surgery *Ann Thorac Surg* 1983;36:389–95.

11 Block PC, Cowley MJ, Kaltenbach M, Kent KM, Simpson J. Percutaneous angioplasty of stenoses of bypass grafts or of bypass graft anastomotic sites *Am J Cardiol* 1984;53:666–8.

12 Laird-Meeter K, Penn OCKM, Haalebos MMP, *et al.* Survival in 1041 patients with consecutive aorto coronary bypass operations. *Eur Heart J* 1984,5. 35–42.

13 Laird-Meeter K, van den Brand MJBM, Serruys PW, *et al* Reoperation after aortocoronary bypass procedure. Results in 53 patients in a group of 1041 with consecutive first operations. *Br Heart J* 1983,50: 157–62.

14 Gruntzig AR, Senning A, Siegenthaler WE Non-operative dilatation of coronary artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979,301:61–7.

15 de Feyter PJ, Serruys PW, van den Brand MJBM, *et al.* Emergency coronary angioplasty in refractory unstable angina. *N Engl J Med* 1985;313:342–6.

16 Brower RW, van Eijk KF, Bos E. Sequential versus conventional coronary artery bypass graft surgery in matched patient groups. *J Thorac Cardiovasc Surg* 1981;29:158–62

17 Hearse DJ, Stewart DA, Braimbridge MV. Cellular protection during myocardial ischemia: the develop-

ment and characterisation of a procedure for the induction of reversible ischemic arrest. *Circulation* 1976;54:193–202.

18 Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc* 1958;53: 457–81.

19 Cox DR. Regression models and lifetables. *J R Soc Med (London)* 1972;34:187–220.

20 Hopkins A. *BMDP statistical software*. Dixon WJ, ed. (1983 printing with addition.) Berkeley: University of California Press, 1983:290–334.

21 Brower RW, Laird-Meeter K, Serruys PW, Meester GT, Hugenholtz PG. Long term follow-up after coronary artery bypass graft surgery. Progression and regression of disease in native coronary circulation and bypass grafts. *Br Heart J* 1983;50:42–7.

22 Forster ED, Fisher LD, Kaiser GC, Myers WO. Principal investigators of CASS and their associates. Comparison of operative mortality and morbidity for initial and repeat coronary artery grafting: the coronary artery study (CASS) registry experience. *Ann Thorac Surg* 1984;38:563–70.

23 Reul GJ, Cooley DA, Coelho A, Chapa L, Eterovic I. Reoperation for recurrent coronary artery disease. Causes, indications and results in 168 patients. *Arch Surg* 1979;114:1269–75.

24 Bourassa MG, Campeau L, Lespérance J, Grondin CM. Changes in grafts and coronary arteries after saphenous vein aortocoronary bypass surgery: results at repeat angiography. *Circulation* 1982;65(suppl II)II:90–7.

25 Chesebro JH, Clements IP, Füster V, *et al.* A platelet-inhibitor-drug trial in coronary-artery bypass operations. Benefit of peri-operative dipyridamole and aspirin therapy on early postoperative vein graft patency. *N Engl J Med* 1983;307:73–8.

26 Campeau L, Enjalbert M, Lespérance J, Vaislic C, Grondin CM, Bourassa MG. Atherosclerosis and late closure of aorto coronary saphenous vein grafts: sequential angiographic studies at 2 weeks, 1 year, 5 to 7 years, and 10 to 12 years after surgery. *Circulation* 1983;68(suppl II)II:1–7.

27 Lawrie GM, Morris GC, Calhoon JH, *et al.* Clinical results of coronary bypass in 500 patients at least 10 years after operation. *Circulation* 1982;66(suppl I) I:1–5.

28 Culliford AT, Girdwood RW, Isom W, Krauss KR, Spencer FC. Angina following myocardial revascularisation. Does time of recurrence predict etiology and influence result of operation. *J Thorac Cardiovasc Surg* 1979;77:889–95.

29 Stiles QR, Cunningham JM. Is re-revascularisation clinically beneficial? *Am J Surg* 1981;141:656–9.

30 Myers WO, Marshfield WI, Davis K, Foster ED, Maynard C, Kaiser GC. Surgical survival in the Coronary Artery Study (CASS) registry. *Ann Thorac Surg* 1985;40:245–60.

31 Cosgrove DM, Loop FD, Lytle BW, *et al.* Determinants of 10-year survival after primary myocardial revascularisation. *Ann Surg* 1985;202:480–8.

32 Varnauskas E, and the European Coronary Surgery Study Group. Survival, myocardial infarction, and employment status in a prospective randomised study of coronary bypass surgery. *Circulation* 1985;72(suppl V)V:90–101.

33 Hartzler GO, Rutherford BD, McConahay DR, Johnson WL, Ligon RW, Calkins MM. "Long-term" clinical results of multiple lesion coronary angioplasty in 500 consecutive patients [Abstract]. *Circulation* 1985;72(suppl III)III:139.

Br Heart J 1987;57:436–45

Clinical, haemodynamic, and antiarrhythmic effects of long term treatment with amiodarone of patients in heart failure

JOHN G F CLELAND, HENRY J DARGIE, IAIN N FINDLAY, JOHN T WILSON

From the Department of Cardiology, Western Infirmary, Glasgow

SUMMARY Twenty two patients with heart failure were studied in a double blind crossover trial to compare amiodarone (200 mg/day) with placebo. Each agent was given for three months. Extrasystoles and complex ventricular arrhythmias were common during ambulatory electrocardiographic monitoring and during exercise testing at entry to the study. Breathlessness and tiredness as assessed by visual analogue scores and duration of treadmill exercise did not become worse during amiodarone treatment. During the placebo and amiodarone phases of the study left ventricular ejection fraction and cardiac index determined by first pass radionuclide ventriculography were similar, both at rest and during upright bicycle exercise. Exercise induced ventricular tachycardia was abolished and simple and complex ventricular arrhythmias observed on 24 hour ambulatory monitoring were greatly diminished during amiodarone treatment. Three patients died, all suddenly, during the placebo phase. In two patients amiodarone was withdrawn after a further myocardial infarction in one and a worsening of symptoms of ventricular arrhythmia in the other.

In contrast with other antiarrhythmic agents amiodarone is effective in suppressing ventricular arrhythmias in heart failure without causing adverse haemodynamic effects. Because frequent ventricular arrhythmias are known to be associated with a poor prognosis in heart failure, these data suggest that amiodarone may improve the poor prognosis in patients with heart failure.

Most patients with chronic heart failure primarily caused by left ventricular dysfunction die suddenly, not from progressively worsening heart failure and pulmonary oedema[1–3] but presumably from ventricular arrhythmias. Asymptomatic ventricular arrhythmias are often found on ambulatory electrocardiographic monitoring[4 5] and several workers have noted an association between their occurrence and the poor prognosis of patients with heart failure[2 4 6] Thus there may be a place for antiarrhythmic treatment in patients with heart failure and ventricular arrhythmias. The negative inotropic effects of many antiarrhythmic agents[7–9] could offset their antiarrhythmic effects.[10] Moreover, class I antiarrhythmic agents have been ineffective in improving prognosis[11] despite evidence that some can reduce the frequency of arrhythmias in patients with heart failure.

Amiodarone, a class III antiarrhythmic agent, has a unique electrophysiological mode of action[12] and in addition is a powerful coronary and peripheral vasodilator.[13 14] Although amiodarone also has been found to have acute negative inotropic effects[15 16] when given in large intravenous doses, which may be due to a non-competitive adrenergic antagonism, this is less apparent during long term use.[15]

We know of no controlled studies on the long term effects of amiodarone in patients with heart failure. In the present study we have investigated the effects of medium term amiodarone treatment on symptoms, exercise performance, left ventricular function, and arrhythmia frequency in a double blind placebo controlled crossover trial.

Patients and methods

We recruited 22 patients (19 men) with heart failure,

Requests for reprints to Dr John G F Cleland, Waller Department of Cardiology, St Mary's Hospital, London W2 1NY

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present for more than six months, into a double blind crossover study with treatment phases (amiodarone or placebo) lasting three months. Ten received amiodarone as the first treatment and 12 placebo. Both treatments were visually identical. The mean (SD) age of the patients was 56 (8) years, the median daily dose of frusemide was 120 mg (range 40–200 mg), mean (SD) end diastolic left ventricular dimension 6·8 (0·9) cm (normal <5·6 cm), and mean (SD) fractional shortening 14·3 (1·5) % (normal >28%). All had stable heart failure; 10 were in New York Heart Association functional class III and 12 were in class II. Sixteen patients were taking digoxin (median daily dose 0·25 mg/day, range 0 0625–0 375), though all were in sinus rhythm. The diagnosis of congestive (dilated) cardiomyopathy in eight and ischaemic heart disease in 14 was established at cardiac catheterisation. Patients were selected because they had heart failure and not because they had serious symptomatic ventricular arrhythmias.

Ten patients were taking captopril, which had been started at least three months before entry to the study (mean 11·8 months, range 4–31 months). Seven others had been taking amiloride and one spironolactone for at least three months because hypokalaemia had developed while they were on diuretics. Amiodarone was adminstered in a dose of 200 mg three times a day for seven days and 200 mg once a day thereafter.

SYMPTOMS

Before the study and at the end of each treatment phase symptoms of breathlessness, tiredness, and ankle swelling were assessed by visual analogue scores

HEART RATE AND BLOOD PRESSURE

Heart rate was counted from the apex beat and blood pressure was recorded in recumbent and standing positions with a Hawkesley Random-zero sphygmomanometer.

ELECTROCARDIOGRAPHY AND EXERCISE TESTING

Ambulatory electrocardiography was performed for 48 hours on a Medilog I system and analysed for isolated ventricular extrasystoles, complex ventricular extrasystoles (bigeminy or two or more consecutive beats), and ventricular tachycardia (three or more consecutive beats at > 120 beats/min). Results are expressed as events per 24 hours. A 12 lead electrocardiogram was also performed at each visit. A treadmill exercise test was carried out according to a modified Bruce protocol. The test was symptom limited.

RADIONUCLIDE VENTRICULOGRAPHY

Radionuclide ventriculograms were obtained at rest and during upright bicycle exercise with a multicrystal gamma camera (Baird Atomic System 77) and a one inch thick parallel hole collimator. After the injection of 300 mBq of technetium-99m counts were recorded at a framing interval of 40 ms (25 frames/s) with the patient resting. A static image was obtained for background correction and exercise was started at a workload of 25 W, increasing by 25 W every three minutes until limited by symptoms. Images were acquired at peak exercise after a further injection of 500 mBq of technetium-99m; counts were recorded at a framing interval of 20 ms (50 frames/s). All radionuclide ventriculograms were corrected for non-uniformity of field by a technetium-99m flood source and for image acquisition during exercise for radiation background from the previous acquisition. The studies were then viewed as serial one second images and frames that included the left ventricle were displayed. A zone of interest representing the left ventricle was defined and a histogram of counts against time was displayed. Because the left ventricular function of the study subjects was poor images of up to eight beats were often obtained before there was appreciable recirculation of radionuclide.

Left ventricular ejection fraction was calculated from the standard formula: end diastolic counts minus end systolic counts divided by end diastolic counts minus background. Background was determined by examining the histogram to identify those frames that occurred immediately before the appearance of the peaks and troughs that are typical of the

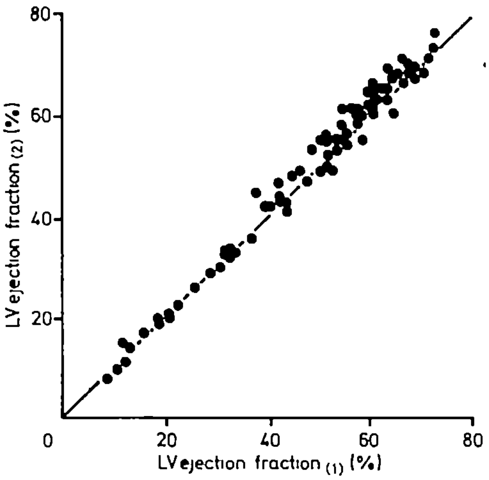

Fig 1 *Intraobserver reproducibility of left ventricular ejection fraction (n = 100; r = 0 99; y = 0 98x + 0 4, standard error of the regression = 2 2%)*

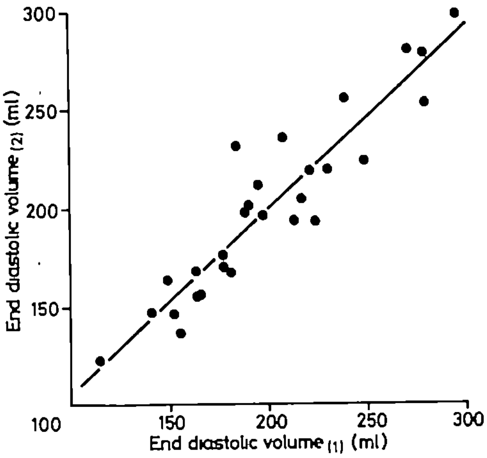

Fig 2 *Intraobserver reproducibility of left ventricular end diastolic volume (n = 30; r = 0·94; y = 0·93x + 14; standard error of the regression = 17 ml).*

left ventricular counts. In our laboratory left ventricular ejection fraction measured by first pass radionuclide ventriculography correlates well with left ventricular ejection fraction measured by contrast angiography (r = 0·86, n = 38). The end diastolic volume was obtained by applying a 21% isocontour to the end diastolic image. The volume was calculated by the Sandler-Dodge area-length method and in 17 subjects it correlated well with the results of contrast angiography (r = 0·9, standard error of the estimate 24 ml). Intraobserver reproducibility for left ventricular ejection fraction is r = 0·99 (fig 1) and for end diastolic volume r = 0 94 (fig 2).

BIOCHEMICAL ANALYSIS

Blood was taken at each visit for the measurement of serum urea, creatinine, digoxin, and electrolytes and also for plasma active renin concentration,[17] angiotensin II,[18] aldosterone,[19] catecholamines,[20] and for thyroid function at baseline and at the end of each treatment phase. Plasma amiodarone concentrations were measured 24 hours after the last dose of the drug. Pulmonary function tests were performed at baseline and at the end of each treatment phase. In addition, patients were assessed clinically at one, two, four, and eight weeks after each change of treatment.

STATISTICAL ANALYSIS

Order and period effects were excluded by comparing the differences between observations for the amiodarone and placebo phases of the two groups by means of two-sample *t* tests; results for the amiodarone and placebo treatment phases were compared by Student's *t* test with log transformation if appropriate. Where sequential observations were made analysis of variance was applied. Correlation coefficients were calculated by the least squares method for normally distributed data.

Results

BASELINE

At entry to the study six of the 22 patients recruited did not have an episode of ventricular tachycardia on 48 hour electrocardiographic monitoring and eight had fewer than 30 ventricular extrasystoles per hour. The median frequency of ventricular extrasystoles in 24 hours was 2487 per 24 hours and of episodes of ventricular tachycardia eight per 24 hours. During exercise all but one of the patients in whom asymptomatic ventricular tachycardia developed were limited by breathlessness or fatigue. Five other patients had episodes of self terminating ventricular tachycardia during exercise testing.

The radionuclide ejection fraction was 20 (9) % at rest and rose to 25 (10) % ($p < 0·05$) on exercise. No patient was hypokalaemic on admission to the study (3·8 (0·3) (3·5–4·6) mmol/l (mean (SD) and range)).

REPRODUCIBILITY OF RADIONUCLIDE DATA

The reproducibility of left ventricular ejection fraction was tested by correlating baseline and placebo data; it was accurate for both rest and exercise studies (figs 3 and 4). Cardiac output during baseline and placebo periods was consistent at rest but less so during exercise (figs 3 and 4). This lack of consistency could not be entirely accounted for by biological variability because the peak exercise heart rates during the two tests were similar.

DOUBLE BLIND STUDY

Symptoms

Table 1 shows that visual analogue scores for breathlessness and ankle swelling were unaffected by amiodarone, whereas tiredness showed a statistically insignificant tendency to increase.

Heart rate and blood pressure (table 1)

Both supine and upright heart rate were significantly lower on amiodarone. After seven days of treatment these two variables were significantly lower on amiodarone than on placebo (fig 5). Systolic blood pressure, supine or erect, was unaltered by amiodarone treatment, though diastolic blood pressure in the supine position alone was lower during amiodarone treatment. No difference in the heart rate or blood pressure response to amiodarone was noted in patients treated with captopril.

Table 1 *Effect of amiodarone on clinical signs and on ventricular arrhythmias in patients in heart failure*

Variable		*Baseline*	*Amiodarone*	*Placebo*
Weight (kg)		70 (10)	69 (9)	69 (9)
Visual analogue scores (mm)				
Breathlessness		36 (21)	26 (14)	29 (17)
Tiredness		33 (15)	36 (17)	25 (15)
Ankle swelling		3 (3)	3 (4)	4 (3)
Blood pressure (mm Hg)				
Supine systolic		121 (16)	120 (17)	118 (14)
Supine diastolic		82 (11)	73 (12)*	78 (9)
Erect systolic		117 (17)	118 (18)	116 (14)
Erect diastolic		88 (10)	76 (11)	87 (13)
Heart rate (beats/min)				
Supine		81 (10)	70 (10)†	79 (12)
Erect		88 (10)	76 (11)†	87 (13)
Ventricular arrhythmias (events/24 h).				
Extrasystoles	Median	979	175‡	900
	Mean	5268	580	3615
	Range	11–35993	0–2397	1–17264
Salvoes	Median	19	2‡	27
	Mean	100	23	101
	Range	0–527	0–132	0–669
Tachycardia	Median	6	0†	9
	Mean	37	5	35
	Range	0–218	0–58	0–217

*Recorded during ambulatory monitoring

Except were stated, values are means (SD).

*p < 0·05, †p < 0·01; ‡p < 0·001 compared with placebo values.

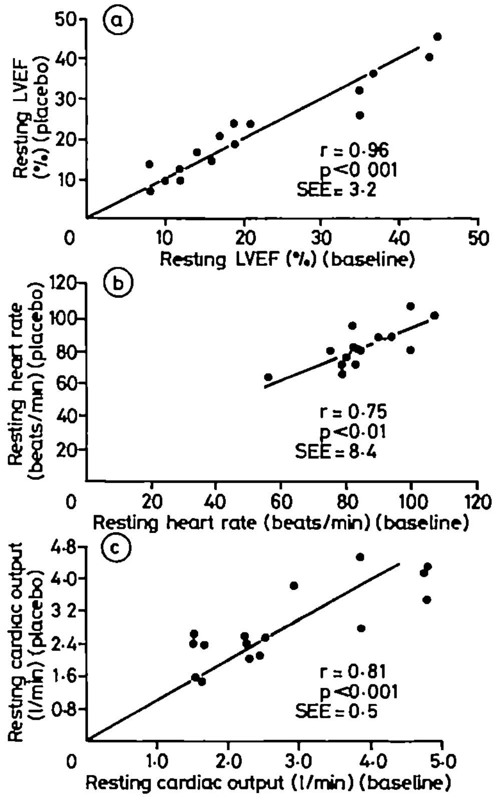

Fig 3 *Correlation of resting values at baseline and during the placebo period. Correlation coefficient and standard error of the estimate (SEE) for (a) resting left ventricular ejection fraction (LVEF), (b) resting heart rate, and (c) resting cardiac output.*

Ambulatory monitoring (table 1)

During amiodarone treatment there was a significant reduction in the frequency of isolated ventricular extrasystoles, complex ventricular extrasystoles, and ventricular tachycardia. There was no difference in arrhythmia control in patients with heart failure of differing aetiologies; but the groups may have been too small for any difference to become apparent.

Exercise testing

During the baseline phase six patients had one or more episodes of non-sustained ventricular tachycardia during their exercise test. Mean (SD) exercise duration was 10·5 (4·2) minutes. There was no difference in mean exercise performance between the amiodarone and placebo phases of the trial (12·1 (3·8) minutes on placebo and 12·8 (3·0) minutes on amiodarone); however, while on amiodarone two patients with ischaemic heart disease performed considerably better and no patient deteriorated. Peak exercise heart rate and systolic blood pressure were unaffected by treatment. In three patients non-sustained ventricular tachycardia developed during the placebo phase but not during treatment with amiodarone. All patients were limited by breathlessness or fatigue during this part of the study. No patient had chest discomfort, nor was any important ST depression seen.

Radionuclide ventriculography (table 2)

The increase in exercise time on amiodarone approached statistical significance (p < 0·07); in a few patients measured during the amiodarone phase the exercise time was considerably longer than dur-

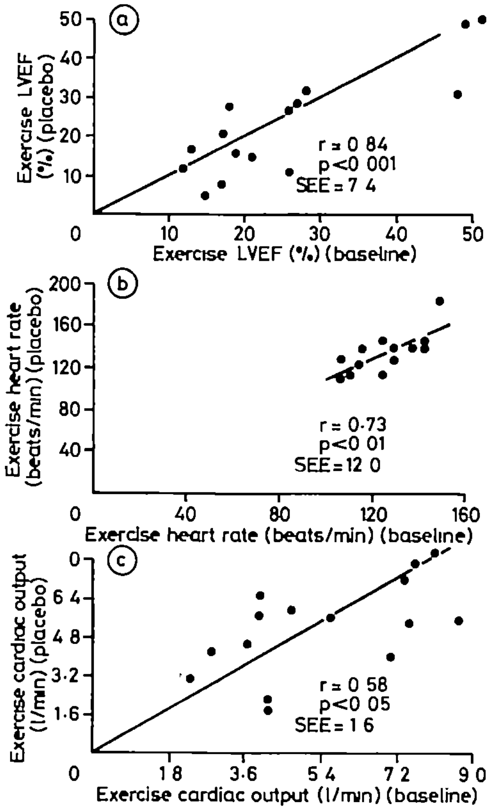

Fig 4 *Correlation of values for variables measured during peak exercise at baseline and during the placebo period. Correlation coefficient and standard error of the estimate (SEE) for (a) left ventricular ejection fraction, (b) heart rate, and (c) cardiac output.*

ing the placebo phase. Heart rate and blood pressure responses were similar during the placebo and amiodarone phases. Rest and exercise ejection fractions were not altered by amiodarone, nor was the increase in ejection fraction during exercise. We found no change in regional wall motion scores and no differences between patients with heart failure caused by ischaemic heart disease and those in whom it had another cause. These groups may have been too small to show any real difference, however.

Biochemistry (table 3)

Concentrations of serum sodium, potassium, urea, and creatinine were unchanged. Plasma concentrations of renin, angiotensin II, aldosterone, and noradrenaline were also unchanged during amiodarone treatment. Serum digoxin rose significantly on amiodarone. Digoxin dosage had been reduced before the study to attain baseline concentrations at the lower end of the therapeutic range. A toxic concentration of serum digoxin was not found in any patient and the dose of digoxin was not altered during the study. During amiodarone treatment serum triiodothyronine concentrations fell while the concentration of serum thyroxine increased. Thyroid stimulating hormone concentrations also increased during amiodarone treatment. Plasma amiodarone concentrations were negligible during the placebo phase of the study.

12 lead electrocardiogram (fig 5)

Heart rate was reduced and QTc prolonged after one and twelve weeks' treatment with amiodarone (fig 5). In most patients the PR interval did not increase.

Table 2 *Haemodynamic variables (mean (SD)) measured during rest and exercise by radionuclide ventriculography*

Variable	*Baseline*	*Amiodarone*	*Placebo*
	Resting values		
Heart rate (beats/min)	85 (12)	73 (13)*	80 (13)
Systolic blood pressure (mm Hg)	113 (21)	115 (19)	115 (16)
Ejection fraction (%)	22 (13)	24 (12)	22 (11)
End diastolic volume index (ml/m)	175 (61)	183 (75)	181 (61)
End systolic volume index (ml/m)	142 (67)	145 (77)	146 (64)
Stroke volume index (ml/m)	33 (13)	38 (12)	35 (11)
Cardiac index (l/m)	2·8 (1·2)	2·7 (0·8)	2·8 (0·9)
Pulmonary transit time (s)	9·2 (2·6)	8·8 (2·8)	9·2 (5·5)
	Exercise values		
Exercise duration (min)	6·1 (1·9)	6·8 (2·2)	5·8 (2·4)
Heart rate	127 (13)	124 (20)	131 (18)
Systolic blood pressure (mm Hg)	150 (30)	156 (29)	151 (20)
Ejection fraction (%)	26 (12)	25 (12)	23 (14)
End diastolic volume index (ml/m)	184 (70)	182 (62)	196 (62)
End systolic volume index (ml/m)	140 (68)	140 (62)	156 (69)
Stroke volume index (ml/m)	44 (15)	42 (15)	39 (15)
Cardiac index (l/m)	5·6 (2·1)	5·1 (1·8)	5·2 (2·1)
Pulmonary transit time (s)	4·4 (3·2)	4·3 (2·9)	4·1 (2·1)

*$p < 0·01$ compared with placebo value.

Table 3 *Results of clinical biochemistry in patients in heart failure treated with amiodarone*

	Baseline	*Amiodarone*	*Placebo*
Serum digoxin (nmol/l)	1 1(0 2)	1 9(0 4)*	1 3(0 2)
Serum creatinine (μmol/l)	106(14)	103(13)	99(18)
Serum sodium (mmol/l)	137(4)	140(2)	139(3)
Serum potassium (mmol/l)	3 8(0 4)	3 9(0 3)	3 8(0 3)
PARC (μU/ml)			
Median	133	134	226
Mean	558	332	578
Range	49–2565	5–1867	47–2768
Plasma angiotensin II (pmol/l)			
Median	23	18	37
Mean	35	50	50
Range	6–124	2–111	11–103
Plasma aldosterone (pmol/l).			
Median	430	294	382
Mean	458	526	446
Range	102–1234	174–1344	83–1271
Plasma noradrenaline (nmol/l)	4 0 (0 6)	2 3(1 6)	3 6(1 5)
Plasma amiodarone (mg/l)		0 8(0 3)	0
Range		0 4–1 3	0–0 1
Plasma desethylamiodarone (mg/l)		0 7(0 2)	0
Range		0 4(1 3)	0–0 1

PARC, plasma active renin concentration.
Except where stated, values are mean (SD)
*p < 0 01 compared with placebo values

Table 4 *Effects of amiodarone on pulmonary function tests, thyroid function, and 12 lead electrocardiography in patients in heart failure*

Variable	*Baseline*	*Amiodarone*	*Placebo*
Pulmonary function tests			
FEV$_1$ FVC (%)	88(16)	93(15)	94(11)
Total lung capacity (%)	97(17)	97(15)	100(15)
Alveolar volume (l)	5 4(0 9)	5 4(1 0)	5 4(1 0)
Transfer factor for carbon monoxide (%)	95(23)	96(14)	98(18)
Thyroid function tests			
Serum triiodothyronine (nmol/l)	1 5(0 4)	1 1(0 2)*	1 4(0 4)
Serum thyroxine (nmol/l)	96(18)	111(22)†	98(20)
Serum thyroid stimulating hormone (U/ml)	2 4(1 3)	4 2(3 4)*	1 8(0 8)
12 lead electrocardiography			
Heart rate (beats/min)	84(11)	72(13)‡	82(13)
PR interval (ms)	178(32)	193(41)	184(38)
QT interval (ms)	345(30)	404(53)*	347(26)
QTc interval (ms)	405(36)	448(49)‡	402(28)

FEV$_1$ FVC, ratio of the forced expiratory volume in one second to the forced vital capacity.
*p < 0 001, †p < 0 05, ‡p < 0 01 compared with placebo values.

Pulmonary function testing (table 4)

Tests of pulmonary function were unaltered by amiodarone.

Clinical outcome

Three patients died during the placebo phase of the study. All died suddenly with no prior worsening of symptoms. All three had both ventricular tachycardia on exercise testing and on 48 hour ambulatory monitoring. All three were taking digoxin; however, serum concentrations at the last clinic visit had been normal. One patient had a myocardial infarction during the amiodarone phase from which he made an uneventful recovery; this patient was withdrawn from the study. In one patient arrhythmias became much worse after a week on amiodarone and this patient was also withdrawn from the study. Subsequent treatment with flecainide caused severe heart failure; reintroduction of amiodarone at a lower dose (200 mg once daily) has been partially effective in controlling his arrhythmias. In one patient episodes of 2:1 heart block developed on amiodarone and these were seen on ambulatory recording. Heart block resolved on placebo. Two patients with left bundle branch block showed no further deterioration in conduction on amiodarone. One patient developed limb paraesthesia without objective neurological signs; this disappeared spontaneously during the placebo phase of the study and subsequently has not recurred on a maintenance dose of 100 mg/day. Good control of arrhythmias

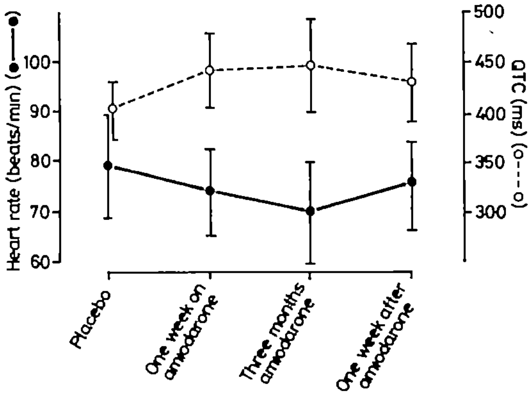

Fig 5 *Sequential analysis (mean (SD)) of QTc and heart rate after one and 12 weeks of amiodarone and after one week of withdrawal of active treatment. Analysis of variance showed a significant ($p < 0{\cdot}01$) change in heart rate and QTc.*

has continued. In each case the combination of captopril and amiodarone was well tolerated.

Discussion

Frequent ventricular extrasystoles are an ominous indicator of a poor prognosis in patients with chronic heart failure caused by left ventricular dysfunction.[2,4,6] As yet there is no evidence that effective suppression of ventricular arrhythmias will prolong the life of a patient with heart failure. An appropriate, effective pharmacological agent is needed to investigate this possibility. Amiodarone is a class III antiarrhythmic agent with antiadrenergic activity[21] that also has a mild direct negative inotropic action that is offset by systemic vasodilatation.[21] The electrophysiological effects of long term oral amiodarone include an increase in the effective refractory period of both atrial and ventricular myocardium and prolongation of atrial and, to a lesser extent, ventricular conduction times.[22,23] Amiodarone reduces sinus node automaticity and thus contributes to a reduction in heart rate.[22] The A-H interval, and probably the H-V interval[22,23] are also prolonged during oral dosing. Amiodarone's antiadrenergic activity is non-competitive, affects both alpha and beta receptor actions, and is probably mediated by a reduction in receptor density or uncoupling of receptors from adenylate cyclase activity.[21,24,25]

As far as we are aware, no controlled studies of the long term safety and efficacy of amiodarone in suppressing arrhythmias in patients with heart failure have been reported. In a short term study in patients with heart failure caused by Chagas's disease there was a mild transient fall in cardiac output and a rise in systemic vascular resistance and left ventricular filling pressure on amiodarone treatment.[26] Other short term studies in patients with coronary artery disease without heart failure have shown an increase in cardiac output and fall in left ventricular end diastolic pressure.[27] Several studies have investigated the effects of long term amiodarone treatment in patients with severe left ventricular dysfunction[27–29]; though these studies have suggested little or no deleterious effect of amiodarone on left ventricular failure they have been uncontrolled and it was not clear that the patients were in heart failure.

In a double blind study we have demonstrated that amiodarone in a relatively low dose of 200 mg/day can appreciably suppress ventricular arrhythmias, both during ambulatory monitoring and during treadmill exercise testing, without worsening symptoms in patients with heart failure of New York Heart Association grade II–III. Moreover, exercise performance and radionuclide ejection fraction both at rest and during exercise were maintained. The negative inotropic effects of amiodarone might have been offset not only by systemic vasodilatation but also by coronary vasodilatation. In the presence of clinically inapparent reversible myocardial ischaemia, which may occur in dilated cardiomyopathy as well as in heart failure caused by ischaemic heart disease, the improvement in the myocardial supply:demand ratio by amiodarone may have maintained cardiac output and ejection fraction.

Resting heart rate was reduced and QTc was prolonged after only one week of amiodarone treatment, which suggests an early onset of electrophysiological action; these effects persisted throughout the 12 week treatment period. The corrected QT interval is thought to correlate with plasma and myocardial concentrations of amiodarone[30,31]; however, the above effects occurred at relatively low concentrations of plasma amiodarone. In the eight patients for whom we have samples, plasma amiodarone concentrations were quite low on a maintenance dose of 200 mg/day.[32] There were several possible explanations for this. Firstly, patients may not have reached steady state concentrations because the half life for elimination of amiodarone is probably more than one month.[32] Amiodarone has a rapid initial distribution phase,[32] and as samples were taken 24 hours after the last dose of amiodarone the measured concentration could have been appreciably lower than the maximum.

The reduction in heart rate on amiodarone was accompanied by a small increase in stroke volume, and because of this there was no change in resting or exercise cardiac output. A fall in systemic vascular resistance may have offset the slightly negative inotropic effect, but we did not demonstrate a reduction in sympathetic activity or renin-angiotensin activity—plasma concentrations of renin and noradrenaline were unchanged.

DRUG INTERACTION

The concentration of serum digoxin increased by 46% in this study and similar results have been obtained by others[33]; symptoms of digoxin toxicity did not occur. This may have been because of the low initial serum digoxin concentration. The rise in serum digoxin that we observed is unlikely to have contributed to the reduction in heart rate and the maintenance of left ventricular ejection fraction. Amiodarone has been used to treat digoxin induced arrhythmias.[34] Amiodarone caused no further significant decline in blood pressure when it was used in conjunction with captopril. This combination seems well suited to the management of patients with heart failure who, as this study shows, commonly have serious arrhythmias. The combined effect of captopril and amiodarone in raising serum digoxin[35] should be noted, but otherwise we noted no other deleterious interaction.

IMPORTANCE OF VENTRICULAR ARRHYTHMIAS IN HEART FAILURE

Many studies have shown that arrhythmias are indicators of a poor prognosis in heart failure[2 4 6] and several studies have also suggested that sudden death is the most common outcome.[4 6] It remains to be proved that arrhythmias are indeed the cause of death, that these are sustained ventricular arrhythmias, and that they can be modified and death prevented by antiarrhythmic agents. Ambulatory electrocardiographic recordings obtained at the time of fatal cardiac arrests suggest that in about 75% of cases this is preceded by a sustained ventricular arrhythmia.[36] Some researchers have related the frequency of these arrhythmias to the extent of left ventricular dysfunction[37 38] and have suggested that, in dictating prognosis, the arrhythmias observed are of secondary importance to the haemodynamic state. Increased sympathetic activity,[39] hypokalaemia,[40] treatment with digoxin,[41] and myocardial cell abnormalities may also contribute to arrhythmias. The relatively poorer prognosis of heart failure caused by coronary artery disease compared with that caused by dilated cardiomyopathy[2] may also suggest that focal myocardial ischaemia is important in the aetiology of arrhythmias; however, subendocardial ischaemia, due to increased myocardial wall tension, can occur in any form of heart failure. Amiodarone has well documented coronary vasodilator actions and these may help to reduce arrhythmias indirectly by improving myocardial perfusion. The suggestion that sympathetic inhibition has a beneficial effect on left ventricular function must remain speculative in view of the controversy over whether β adrenergic receptor blockade is helpful in heart failure.[42 43]

According to the Framingham study 4% of the population under the age of 75 will develop heart failure before death[44] In Britain this would account for 60 000 new cases of heart failure per year. In Scotland alone there were over 6000 deaths in 1983 in which heart failure was a contributory cause (personal communication, Registrar General, New Registrar House, Edinburgh, Scotland). Though cardiac transplantation may be the most successful treatment for very poor left ventricular function, the problem is so large that transplantation is excluded in most patients. Patients with lesser degrees of heart failure also have a high annual mortality and alternative medical treatment is required to improve not only their symptoms but also their prognosis.

EFFECTS OF TREATMENT

The effect of an antiarrhythmic agent on the prognosis in heart failure has been investigated in another controlled trial.[11] In that study procainamide did not improve prognosis; however, the groups were not randomly allocated to treatment and the efficacy of arrhythmia suppression was not commented on. We are unaware of any previous study that has investigated concurrently the long term haemodynamic and electrophysiological effects of antiarrhythmic drugs in heart failure. Some antiarrhythmic drugs such as disopyramide and flecainide seem to be unsuitable for use in heart failure because of their negative inotropic action.[7 8] As agents such as β blockers and verapamil have negative inotropic effects, they too seem less attractive; however, there are reports of a beneficial effect of β blockers in heart failure.[42 43]

SIDE EFFECTS

Because amiodarone has a long half life the dose may require careful titration and the regimen may have to be altered even after long term treatment. Arrhythmias can become worse in patients on amiodarone,[45] often with the first few doses; this is possibly a consequence of its class I activity.[46] Therefore, careful patient monitoring is required initially. We have encountered patients who are intolerant of 200 mg/day because of gastrointestinal side effects and rhythm disturbances, some require $\leqslant$100 mg/day to control their arrhythmias. One patient in this study developed much more frequent arrhythmias on the loading dose of 600 mg/day but after withdrawal from the study he improved on a dose of 200 mg/day. In another patient in this trial conduction disturbances developed at a dose of 200 mg/day when the serum concentration of amiodarone was only 0·5 mg/l. Patients with heart failure may be more sensitive to the effects of amiodarone. Left bundle branch block does not seem to be a contraindication to treatment, however, and this is confirmed by the experience of others.[47]

After three months' treatment with amiodarone we noted a significant fall in serum triiodothyronine and rise in thyroid stimulating hormone, implying a mildly hypothyroid state. None the less, no patient developed clinical signs of hypothyroidism, which accords with the small increase in the concentration of thyroid stimulating hormone. The assay for thyroid stimulating hormone is insensitive at low concentrations, however, and this result should be interpreted with caution. We found no clinical or biochemical evidence of hyperthyroidism in this study. The mechanism by which amiodarone blocks the conversion of thyroxine to triiodothyronine has been reviewed elsewhere.[48] Tests of pulmonary function were unaffected by amiodarone, perhaps because the duration of treatment was short.[49] One patient developed symptoms suggestive of peripheral neuropathy on 200 mg/day. After the study he continued to take amiodarone 100 mg/day with resolution of symptoms and continuing arrhythmia control. These and other side effects of amiodarone have been well reviewed by Harris *et al* and McKenna *et al.*[50,51]

In conclusion, amiodarone seems to be an effective treatment for arrhythmias in heart failure and does not worsen symptoms or exercise tolerance. Its use in conjunction with captopril appears to be safe. Occasional patients may have worsening of their arrhythmias after amiodarone; this appears early after its introduction and close supervision is recommended to prevent adverse reactions.

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References

1 Meinertz T, Hofmann T, Kasper W, *et al* Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Am J Cardiol* 1984,**53**:902–7.

2 Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary artery disease or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1983;**51**. 831–6.

3 Cohn JN, Levine TB, Olivari MT, *et al.* Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;**311**:819–23.

4 Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy *Am J Cardiol* 1984;**54**:147–52.

5 McKenna WJ, Krikler DM, Goodwin JF. Arrhythmias in dilated and hypertrophic cardiomyopathy. *Med Clin North Am* 1984;**68**:983–1000.

6 Holmes J, Kubo SH, Cody RJ, Kligfield P. Arrhythmias in ischemic and nonischemic dilated cardiomyopathy: prediction of mortality by ambulatory electrocardiography *Am J Cardiol* 1985;**55**:146–51.

7 Josephson MA, Kaul S, Hopkins J, *et al.* Hemodynamic effects of intravenous flecainide relative to the level of left ventricular function in patients with coronary artery disease. *Am Heart J* 1985;**109**:41–5.

8 Sutton R. Haemodynamics of intravenous disopyramide. *J Int Med Res* 1976;**4**(suppl 1):46–8.

9 Ferlinz J, Easthope JL, Aronow WS. Effects of verapamil on myocardial performance in coronary artery disease. *Circulation* 1979;**59**.313–9

10 Robinson C. Haemodynamic effects of atenolol in patients with coronary artery disease. *Br Heart J* 1978;**40**:22–8.

11 Chakko CS, Gheorghiade M. Ventricular arrhythmias in severe heart failure: incidence, significance, and effectiveness of antiarrhythmic therapy. *Am Heart J* 1985;**109**:497–504.

12 Singh BN, Vaughan-Williams EM. The effects of amiodarone, a new anti-anginal agent drug of cardiac muscle. *Br J Pharmacol* 1970;**39**:657–67.

13 Côté P, Bourassa MG, Delaye J, Janin A, Froment R, David P Effects of amiodarone on cardiac and coronary hemodynamics and on myocardial metabolism in patients with coronary artery disease. *Circulation* 1979;**59**:1165–72.

14 Singh BN, Jewitt DE, Downey JM, Kirk ES, Sonnenblick EH. Effects of amiodarone and L8040, novel antianginal and antiarrhythmic drugs, on cardiac and coronary hemodynamics and on cardiac intracellular potentials. *Clin Exp Pharmacol Physiol* 1976;**3**:427–42.

15 Pfisterer M, Burkart F, Muller-Brand J, Kiowski W. Important differences between short- and long-term effects of amiodarone in patients with chronic ischemic heart disease at rest and during ischemia-induced left ventricular dysfunction. *J Am Coll Cardiol* 1985;**5**:1205–11.

16 Schwartz A, Shen E, Morady F, Gillespie K, Schienman M, Chatterjee K. Hemodynamic effects of intravenous amiodarone in patients with depressed left ventricular function and recurrent ventricular tachycardia. *Am Heart J* 1983;**106**:848–55.

17 Millar JA, Leckie BJ, Semple PF, Morton JJ, Sonkodi

S, Robertson JIS. Active and inactive renin in human plasma: renal arteriovenous differences and relationship with angiotensin and renin substrates. *Circ Res* 1978;**43**(suppl 1):120–7.

18 Atkinson AB, Morton JJ, Brown JJ, *et al.* Captopril in clinical hypertension. Changes in components of renin-angiotensin system and in body composition in relation to fall in blood pressure with a note on measurement of angiotensin II during converting enzyme inhibition. *Br Heart J* 1980;**44**:290–6.

19 Fraser R, Guest S, Young J. Comparison of double isotope derivative and radio-immunological estimation of plasma aldosterone concentration. *Clin Sci Mol Med* 1973;**45**:411–5.

20 Ball SG, Tree M, Morton JJ, Inglis GC, Fraser R. Circulating dopamine: its effect on the plasma concentrations of catecholamines, renin, angiotensin, aldosterone and vasopressin in the conscious dog. *Clin Sci* 1981;**61**:417–22.

21 Charlier R. Cardiac actions in the dog of a new antagonist of adrenergic excitation which does not produce competitive blockade of adrenoreceptors. *Br J Pharmacol* 1970;**39**:668–74.

22 Finermann WB, Hamer A, Peter T, Weiss D, Mandel WJ. Electrophysiologic effects of chronic amiodarone therapy in patients with ventricular arrhythmias. *Am Heart J* 1982;**104**:987–96

23 Wellens HJJ, Brugada P, Roy D, Heddle B, Bar FW. A comparison of the electrophysiological effects of intravenous and oral amiodarone [Abstract]. *Am J Cardiol* 1982;**49**:1043.

24 Sharma AD, Corr PB. Modulation by amiodarone of cardiac adrenergic receptors and their electrophysiologic responsivity to catecholamines [Abstract]. *Circulation* 1983;**68**(suppl III):99

25 Gagnol JP, Devos C, Clinet M, Nokin P. Amiodarone: biochemical aspects and haemodynamic effects. *Drugs* 1985;**29**(suppl 3):1–10.

26 Bellotti G, Silva LA, Filho AE, *et al.* Haemodynamic effects of intravenous administration of amiodarone in congestive heart failure from chronic Chagas' disease. *Am J Cardiol* 1983;**52**:1046–9.

27 Greene HL, Graham EL, Werner JA, *et al.* Toxic and therapeutic effects of amiodarone in the treatment of cardiac arrhythmias. *J Am Coll Cardiol* 1983;**2**: 1114–28.

28 Trobaugh GB, Kudenchuk PJ, Green HL, *et al.* Effect of amiodarone on ventricular function as measured by gated radionuclide angiography. *Am J Cardiol* 1984;**54**:1263–6.

29 Ellenbogen KA, O'Callaghan WG, Colavita PG, Smith MS, German LD. Cardiac function in patients on chronic amiodarone therapy. *Am Heart J* 1985;**110**:376–81.

30 Debbas NMG, du Cailar C, Sassine A, Derancourt J, Demaille JG, Puech P. Determination of cardiac and plasma drug levels during long-term amiodarone therapy. *Eur J Clin Invest* 1983;**13**:123–7.

31 Debbas NMG, du Cailar C, Bexton RS, Demaille JG, Camm AJ, Puech P. The QT interval: a predictor of the plasma and myocardial concentration of amiodarone. *Br Heart J* 1984;**51**:316–20.

32 Holt DW, Tucker GT, Jackson PR, Storey GCA. Amiodarone pharmacokinetics. *Am Heart J* 1983; **106**:840–7.

33 Moysey JO, Jaggarao NSV, Grundy EN, Chamberlain DA. Amiodarone increases plasma digoxin concentrations. *Br Med J* 1981;**282**:272.

34 Maheswaran R, Bramble MG, Hardisty CA. Massive digoxin overdose: successful treatment with intravenous amiodarone. *Br Med J* 1983;**287**.392–3.

35 Cleland JGF, Dargie HJ, Pettigrew A, Gillen G, Robertson JIS. The effect of captopril on serum digoxin and urinary digoxin clearance in patients with heart failure. *Am Heart J* 1986;**112**:130–5.

36 Milner PG, Platia EV, Reid PR, Griffith LSC. Ambulatory electrocardiographic recordings at the time of fatal cardiac arrest. *Am J Cardiol* 1985,**56**.588–92.

37 Diaz R, Obasohan A, Newman H, Goodwin JF, Oakley C. Prognostic indicators in dilated cardiomyopathy [Abstract]. *Br Heart J* 1985;**53**·114.

38 von Olshausen K, Schäfer A, Mehmel HC, Schwarz F, Senges J, Kubler W. Ventricular arrhythmias in idiopathic dilated cardiomyopathy. *Br Heart J* 1984; **51**:195–201.

39 Reddy CP, Gettes LS. Use of isoproterenol as an aid to electrical induction of chronic recurrent ventricular tachycardia. *Am J Cardiol* 1979;**44**:705–13.

40 Hollifield JW, Slaton PE, Moore LC. Diuretic treatment of hypertension: hypokalaemia and cardiac arrhythmias complicating thiazide therapy. *International Medicine* 1983;**5**(suppl):127–31.

41 Shapiro W. Corrective studies of serum digitalis levels and the arrhythmias of digitalis intoxication. *Am J Cardiol* 1978;**41**:852–9.

42 Waagstein F, Hjalmarson Å, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J* 1975;**37**:1022–36.

43 Taylor SH, Silke B. Haemodynamic effects of beta-blockade in ischaemic heart failure. *Lancet* 1981; **ii**:835–7.

44 McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;**285**:1441–6.

45 Sclarovsky S, Lewin RF, Kracoff O, Strasberg B, Arditti A; Agmon J. Amiodarone-induced polymorphous ventricular tachycardia. *Am Heart J* 1983;**105**:6–12.

46 Cobbe SM, Manley BS. Cellular electrophysiology of amiodarone in cardiac ischaemia. *Br J Clin Pract* 1986;**40**:104–6.

47 Kaski JC, Girrotti LA, Messuti H, Rutitzky B, Rosenbaum MB. Long-term management of sustained, recurrent, symptomatic ventricular tachycardia with amiodarone. *Circulation* 1981;**64**:273–9.

48 Sanmarti A, Permanyer-Miralda G, Castellanos JM, Foz-Sala M, Galard RM, Soler-Soler J. Chronic administration of amiodarone and thyroid function: a follow up study. *Am Heart J* 1984;**108**:1262–8.

49 Kudenchuk PJ, Pierson DJ, Greene HL, Graham EL, Sears GK, Trobaugh GB. Prospective evaluation of amiodarone pulmonary toxicity. *Chest* 1984;**86**: 541–4.

50 Harris L, McKenna WJ, Rowland E, *et al.* Side effects of long-term amiodarone therapy. *Circulation* 1983; **67**:45–51.

51 McKenna WJ, Rowland E, Krikler DM. Amiodarone: the experience of the past decade. *Br Med J* 1983;**287**:1654–6.

Br Heart J 1987;57:446–57

Coronary disease, cardioneuropathy, and conduction system abnormalities in the cardiomyopathy of Friedreich's ataxia*

THOMAS N JAMES,† B WOODFIN COBBS,‡ H CECIL COGHLAN,†
WALTER C McCOY,† CHARLES FISCH§

From the †University of Alabama School of Medicine, Birmingham, Alabama, the ‡Emory University School of Medicine, Atlanta, Georgia, and the §University of Indiana School of Medicine, Indianapolis, Indiana, USA

SUMMARY Abnormalities of the heart are a frequent and possibly ubiquitous problem in patients with Friedreich's ataxia, but their pathogenesis is unclear. Postmortem findings are reported from the hearts of three patients with Friedreich's ataxia who died of congestive heart failure and atrial arrhythmias. Particular attention was paid to the following: the large and small coronary arteries, the nerves and ganglia, the conduction system, and the histological and cellular features of the cardiomyopathy. There were pleomorphic nuclei and focal fibrosis and degeneration throughout each heart including the conduction system. There were distinctive abnormalities of both large and small coronary arteries, and focal degeneration of nerves and ganglia. These observations suggest a mosaic concept for the pathogenesis for the cardiomyopathy of Friedreich's ataxia that involves the interplay of molecular faults, cardiomyopathy, cardioneuropathy, and coronary disease.

In Friedreich's original description of the heritable ataxia that now bears his name he reported that five of his six cases showed clinical evidence of heart disease.[1] Although the existence of such heart disease has been recognised for many years—and despite Friedreich's own experience—it has only recently come to be widely appreciated how often the heart is abnormal in these ataxic individuals. Current estimates in two large series of carefully studied cases suggest that between 90% and 100% of patients with definite Friedreich's ataxia will have some demonstrable abnormality of the heart, whether or not any clinical cardiac manifestations have yet appeared.[2 3]

Despite the continuing investigations of heart disease of Friedreich's ataxia,[4−31] uncertainty about its pathogenesis remains. It is known that affected individuals may develop cardiac hypertrophy of either the symmetrical or asymmetrical type and with or without dilatation, that they eventually have progressively increasing congestive heart failure which is often the cause of death, and that their clinical course is characterised by the occurrence of arrhythmias and various other forms of electrical instability of the heart. But these clinical descriptive features are of little help in determining the fundamental basis of the heart disease; and without that knowledge it will continue to be difficult to determine prognosis or to develop optimal forms of treatment.

Previous studies have unequivocally shown that the small coronary arteries are abnormal in patients who have cardiac disease and Friedreich's ataxia[5 6 8−12]; but the functional significance of this finding has been challenged, particularly by Hewer[11] whose findings have been widely quoted in virtually all subsequent reviews. In the present report we describe our own findings in three patients, which support the importance of small coronary artery disease, and show why we believe that Hewer's personal observations do in fact accord our findings.

A second cardiac abnormality originally described by Dorothy Russell,[5] who may also have been the

Requests for reprints to Dr Thomas N James, Callaway Laboratory of the Department of Medicine, University of Alabama Medical Center, Birmingham, Alabama 35294, USA.

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first to call attention to the coronary disease in her case 3, is a form of myocarditis which we believe is better regarded as a form of cardiomyopathy. While the cardiomyopathy is undoubtedly influenced by disease of the small coronary vessels, cardiomyopathy seems unlikely to be explained entirely by such disease.

The third abnormality that is abundantly present is cardioneuropathy, which we believe is described for the first time in this report. A fourth component of our study deals with the conduction system of the heart, abnormalities of which help to explain the frequent manifestations of cardiac electrical instability in these patients. We believe that interdependent relations of all these factors form the basis for a mosaic concept of the pathogenesis of heart disease in patients with Friedreich's ataxia.

Clinical observations

CASE 1

This twenty year old white man was first found to have Friedreich's ataxia at about the age of eight, and within two years intermittent heart failure that was responsive to treatment with conservative measures developed. Over the next decade his cardiac failure progressed only gradually, although several bouts were transiently severe. These were often associated with episodes of pulmonary infection. He was usually in sinus rhythm with multiple atrial extrasystoles, but several bouts of atrial fibrillation were documented, especially in his last year of life. The terminal illness was characterised by an abrupt onset of severe hypotension accompanied by cyanosis and dyspnoea. It was briefly and incompletely responsive to treatment with digitalis, diuretics, and similar measures. He died eight days after the onset of hypotension.

CASE 2

A twenty two year old white man was first diagnosed as having Friedreich's ataxia at the age of six. In the last five years of his life he had recurring bouts of atrial flutter and fibrillation that were eventually associated with steadily worsening congestive heart failure. Several episodes of pulmonary infection complicated cardiac disease. During this time he complained of a dull substernal non-radiating pain, which lasted 10 to 15 minutes. It was often produced by emotional stress. He was too disabled to undertake any activity that was physically taxing. His final admission was for severe pulmonary congestion which became intractable and led to cyanosis and coma. He died the next day.

CASE 3

This twenty year old white man had Friedreich's ataxia with progressive cardiac failure for five years. There were intermittent bouts of atrial fibrillation. Recurring episodes of pulmonary infection aggravated the cardiac insufficiency. During his last admission the congestive failure was more severe and there was atrial flutter with partial heart block. He died quietly on the fifth hospital day. Other details of this case have been reported before.[8] It is included here after further assessment of the coronary disease and a special study of the nerves and ganglia of the heart, which were not a subject of the previous study.

Morphological observations

In all three cases the heart was generally enlarged but not much dilated. Gross heart weights for cases 1, 2, and 3 were 470 g, 495 g, and 550 g respectively. All three cases had extensive pulmonary and other visceral congestion, varying amounts of bronchopneumonia, and histological evidence of spinocerebellar degeneration. Within the hearts there was no valve disease, the interatrial and interventricular septa were intact, and there were no gross

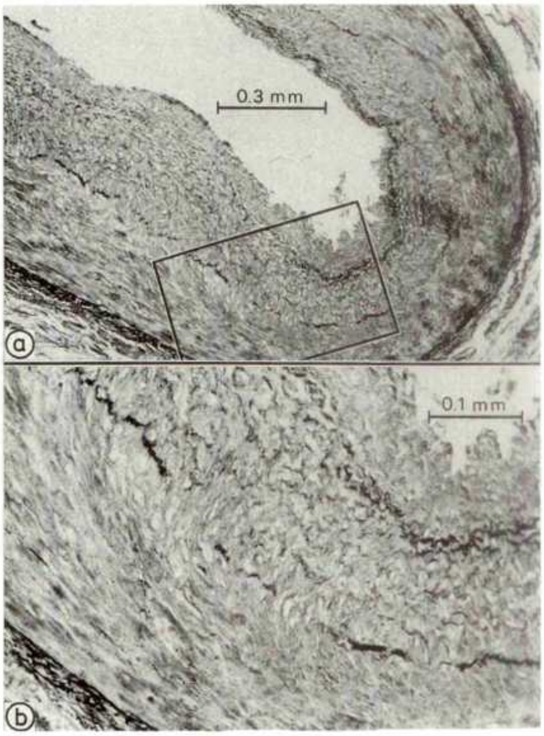

Fig 1 *Photomicrographs showing focal fibromuscular dysplasia of the main right coronary artery shown at two magnifications (a and b). Verhoeff-van Gieson elastic stain. All magnifications are indicated by reference bars.*

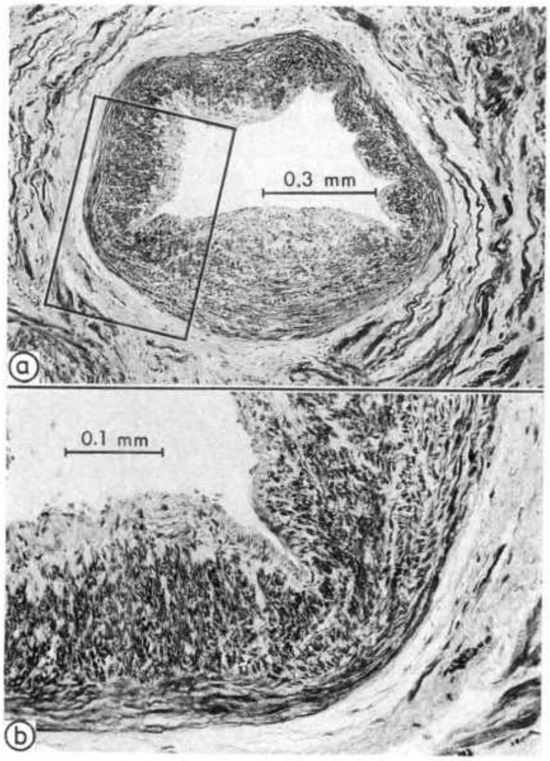

Fig 2 *Photomicrographs showing focal fibromuscular dysplasia of the sinus node artery at two magnifications (a and b). This section and all subsequent sections are stained with Goldner trichrome unless stated otherwise.*

anomalies or malformations. In each case the pericardium was slightly fibrotic, especially in cases 1 and 3, but there was no active pericarditis and there were no important adhesions.

Because there was atrial arrhythmias in all three cases the sinus node, atrioventricular node, and His bundle were examined.[32 33] In addition to tissue removed for examination of the conduction system, we also examined four slices of left ventricle (minimal size 15 by 40 mm), four of right ventricle (at least 10 by 40 mm), and two of left atrium (at least 5 by 25 mm). The sinus node sections included considerable amounts of right atrium. At least 10 serial 2 mm slices of sinus node were available from each case. The sections of atrioventricular node and His bundle included at least 2 cm of both atrial and ventricular septal tissue, and for each case there were at least eight 2 mm slices cut serially from this region. From each of these tissue slices at least 10 serial sections of 8 µm thickness were prepared with the Goldner trichrome stain; additional sections were stained with the periodic acid Schiff, Verhoeff-van Gieson elastic, and congo red methods.

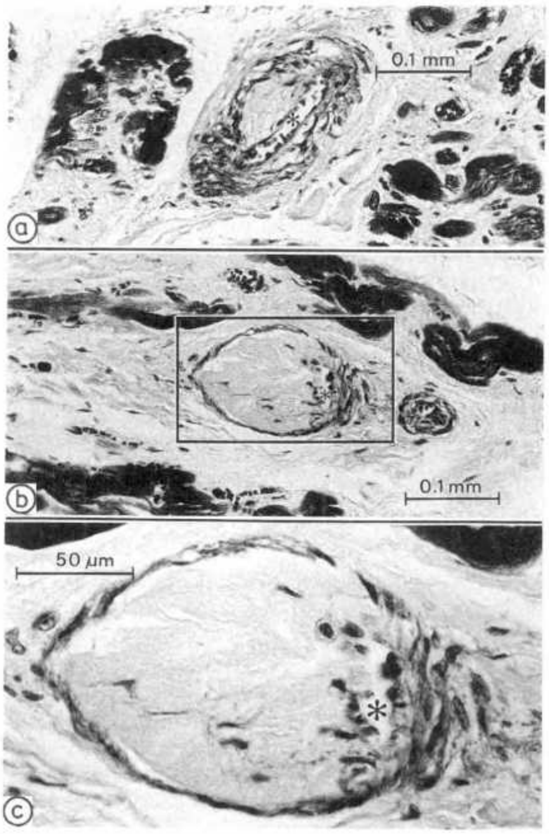

Fig 3 *Photomicrographs showing abnormalities of the small coronary arteries in branches of the atrioventricular node artery. The lumen (asterisk) in (a) is narrowed by an intramural amorphous deposit and there is degeneration of the tunica media. (b) Only thin tunica media remains, with an even larger amorphous intramural deposit in the artery. This is shown at higher magnification in (c). The tiny lumen remaining is indicated by an asterisk.*

As part of the light microscopic examinations at least 400 colour photomicrographs were prepared of each of the three cases. Study of both these and the histological slides showed that the myocardial, neural, and arterial lesions were similar in nature and distribution in each case. Black and white photomicrographs from case 1 were then prepared; they are representative of all three cases. The important categories of abnormalities are the coronary disease, the cardioneuropathy, and the conduction system as well as a probably separate myocytopathy of the heart.

CORONARY DISEASE

In the previous report of case 3 an abnormality of one

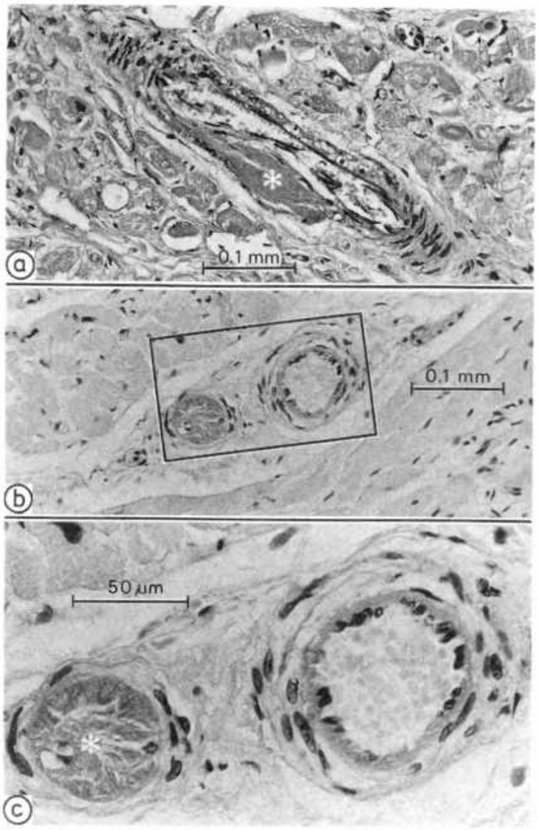

Fig 4 *Photomicrographs showing staining of the amorphous intramural deposits in small coronary arteries by periodic acid-Schiff. In the tangentially cut artery (a) the deposit is marked with a white asterisk. There is one patent artery and one that is nearly occluded (b). These are shown at higher magnification (c). The dark Schiff-positive material is marked with a white asterisk.*

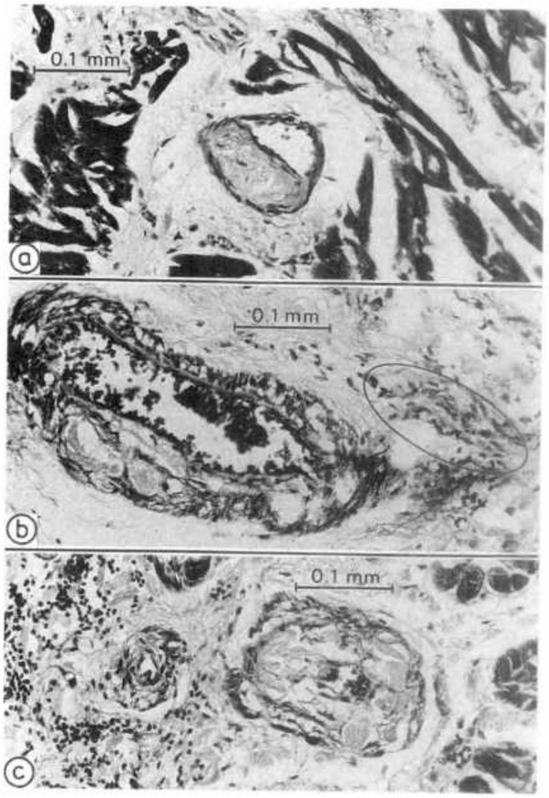

Fig 5 *Photomicrographs showing material stained with periodic acid-Schiff stain without much associated degeneration in some vessels (a) and extensive association with medial degeneration, which is often but not always cystic in nature (b and c), in others. A small degenerating nerve is circled in (b). The artery in (a) is in the interventricular septum, the one in (b) is in the interatrial septum, and the one in (c) is near the sinus node.*

large coronary branch was briefly mentioned. This result, the description by Dorothy Russell of constricting atheromas in the large and small coronary arteries of her case 3 (a 21 year old man) and similar findings by Lamarche *et al*,[12] and the recent report of clinically important coronary spasm in Friedreich's cardiomyopathy[29] prompted a careful examination of the large coronary arteries of our three cases. In addition to preparing cross sections at intervals of no more than 5 mm within all three major coronary trunks for gross examination, we examined histological sections taken from at least four equidistant sites within the three main coronary arteries, beginning at the origin of each artery. In all three hearts we found three or more sites of narrowing without occlusion of two or more major coronary trunks (that is those that were at least 1·5 mm in diameter). At no point was there any coronary thrombosis nor any typical atheroma formation nor endothelial ulceration or fissuring. Although some stenotic lesions showed intimal proliferation, the principal cause of narrowing was focal fibromuscular dysplasia (figs 1 and 2). None of the large coronary arteries showed the special Schiff positive intramural lesion often found in small coronary arteries.[8]

A wide range of histological abnormalities have been reported in stenosis of the small coronary arteries.[8] All types of these lesions were focal in distribution; for example serial examination of sections from the same small artery always disclosed some normal segments even when there was indisputable disease in another area (figs 3–6). The following histological abnormalities were found: medial degeneration and fibrosis; intimal proliferation; focal

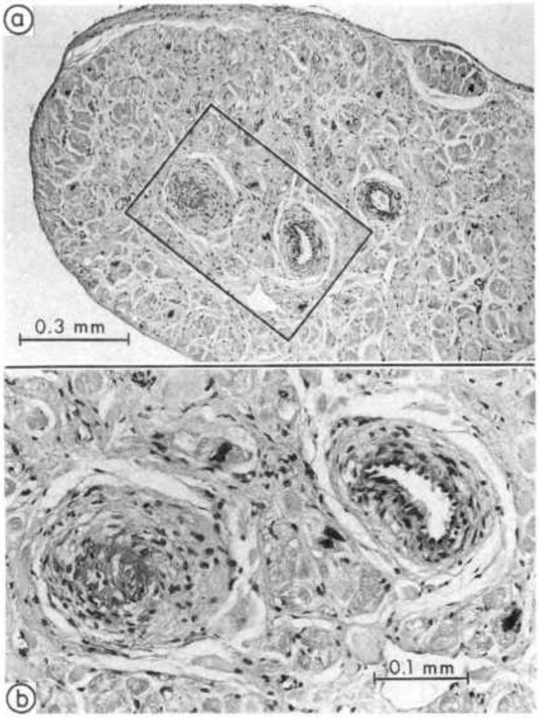

Fig 6 *Photomicrographs of three small arteries in the crista terminalis, all branches of the sinus node artery, showing a range of abnormalities. The two more distinctly abnormal ones are boxed in (a) and seen at higher magnification in (b). A subintimal deposit of material stained by periodic acid-Schiff reagent is evident in the artery to the left in (b) and smaller amounts are seen scattered in a neighbouring artery.*

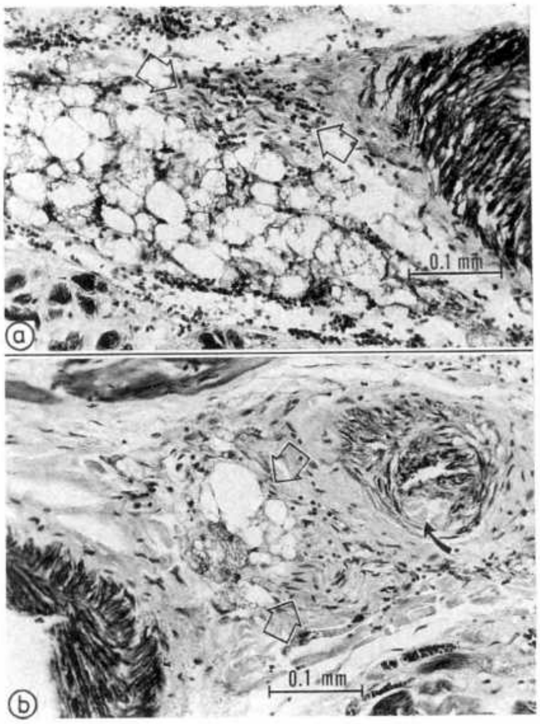

Fig 7 *Photomicrographs showing two examples (a and b) of neural degeneration near the sinus node. Neural tissue is indicated by open arrows. Amorphous intramural deposit within a small artery is indicated by curved arrow in (b).*

fibromuscular dysplasia; and either subintimal or medial deposition of an amorphous material stained by periodic acid-Schiff method. The last three abnormalities all produced luminal narrowing. These four histological abnormalities were demonstrable in all of the three cases, and sometimes in different segments of the same artery (for example in the sinus node artery, atrioventricular node artery, or the long branches in the interventricular septum). Inflammation was rarely seen in the arteries and when it was it was only slight.

So that we could compare our results with those of Hewer[11] we examined at least 100 cross sections of coronary arteries from subserial sections of the interatrial and interventricular septa, like those that are routinely prepared for study of the atrioventricular node and His bundle. When we used Hewer's criterion of >50% narrowing of an arterial lumen as being "functionally significant" (a point which we dispute), we found, as he did, approximately 9% of such narrowings. In these three cases lesions causing >50% narrowing were found in 5% to 8% of examined sections of small arteries. When 100 consecutively encountered cross sections of small coronary arteries of the left ventricular slices were examined, we found that only 3–5% showed narrowing of ≥50%. In all myocardial samples studied there were structural abnormalities of the small coronary arteries (not causing 50% narrowing) in 35–40% of cross sections of arteries that were between 100 and 1000 μm in diameter. Later we will explain why these lesions cannot be regarded as functionally insignificant.

The nature of the Schiff positive material characteristically found in the small coronary arteries of Friedreich's cardiomyopathy is not known. We wonder why others do not appear to have sought this lesion. Morphologically it resembles deposits of amyloid, but neither in the original description[8] nor in specially prepared congo red stains of these three cases for the present report was there any specific staining for amyloid. Similarly, stains for fat or fibrin have been consistently negative. Small deposits of this Schiff-positive material were found rarely in a nerve or within myocytes, but the material was most

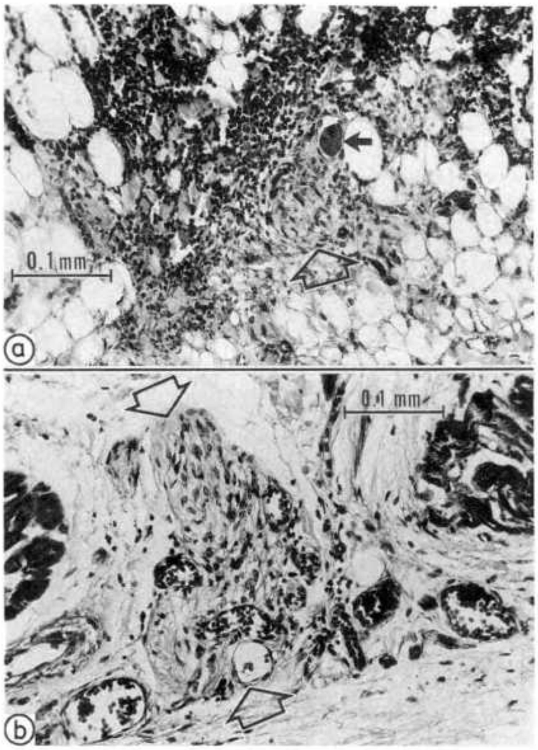

Fig 8 *Photomicrographs showing haemorrhagic degeneration of a nerve (open arrow) in the sinus node (a) with one ganglion cell indicated by a black arrow. A degenerating nerve near the atrioventricular node is indicated by two open arrows (b).*

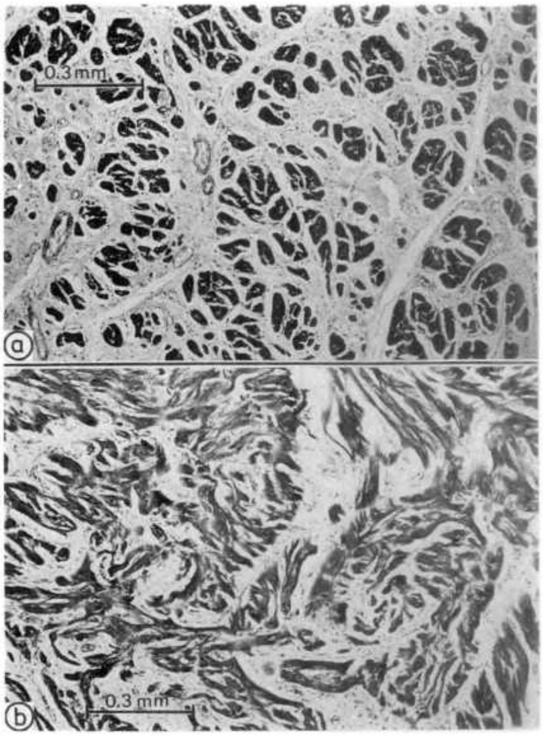

Fig 9 *Photomicrographs showing focal fibrosis (a) in the posterior papillary muscle of the left ventricle. (b) Fibre disarray intermingled with some fibrosis within the interventricular septum.*

often and readily demonstrable in the small coronary arteries. Dr Alexander Nadas kindly gave us the opportunity of examining sections of the original case of Nadas *et al.*[6] The stenotic lesions in the small coronary arteries also contained Schiff positive material. As in our own cases, however, the Nadas case also had other histological lesions that narrowed the small coronary arteries but did not contain Schiff positive material.

CARDIONEUROPATHY

We especially studied nerves and ganglia in the conduction system, where they are abundant. In all three hearts there was extensive focal degeneration of the myelinated and unmyelinated nerves and the cardiac ganglia (figs 5, 7, and 8). Some of these examples were associated with a moderate degree of round cell infiltration whereas others showed principally fragmentation and necrosis without much cellular response. In addition to the neural lesions that were easily demonstrable within and near the conduction system we found similar neural abnormalities within both the right and left ventricular myocardium. Because we studied at least 10 serial sections from every tissue block we could be certain that the neural lesions were focal. Relatively normal nerve tissue was often present 30 or 40 μm away from an extensively diseased area. Interruption of a nerve at any point can be functionally important for the entire nerve.

We did not use special stains to determine whether the observed neural lesions occurred in sympathetic or parasympathetic nerves. Special silver impregnation stains have no significant advantage over the demonstration of cardiac neural structures with the Goldner trichrome stain.[34] Because most ganglia within the heart are considered to be components of the vagal system, we assume that the lesions of ganglia occurred in parasympathetic units. Local nerves were included in some regions of myocardial degeneration, but cardioneuropathy was also often found as isolated degeneration with no neighbouring myocardial disease. In cross section small coronary arteries characteristically have paired nerves flanking them,[34] especially in the atria. Although there were juxta-arterial lesions of nerves accompanying some arterial lesions, the two abnormalities were often found separately, that is neural lesions were found away from arteries and abnormal arteries had local nerves of normal appearance.

CONDUCTION SYSTEM

There were distinct and consistent abnormalities of the conduction system in all three hearts. In each the sinus node (figs 2, 5, 6, and 8) was more affected than the atrioventricular node or the His bundle. There were focal narrowings of local arteries both in the sinus node and the atrioventricular junctional region, and cardioneuropathy was also found at both sites. Within the three sinus nodes there was focal degeneration and fibrosis, attributable in part to the coronary disease but also separate from it. For example, the bizarre pleomorphic nuclei seen in myocytes outside the conduction system were also present within it, particularly in the sinus node. The His bundle was generally intact in all three cases and was the least affected component of conduction system. In case 2 focal degeneration in the atrioventricular node almost equalled that seen in the sinus node, but in cases 1 and 3 the atrioventricular node was only slightly affected. Since all three cases had clinically significant atrial arrhythmias, the presence and extent of disease in the sinus node and adjacent atrial myocardium must be interpreted as being functionally important.

CARDIOMYOPATHY AND MYOCYTOPATHY

None of the three hearts showed hypertrophy of more than moderate degree, nor was hypertrophy asymmetrically distributed. There were occasional examples of disarray of myocardial fibres (fig 9), but no more than is readily found in almost any form of cardiac hypertrophy. The two principal histological abnormalities of myocardium were focal fibrosis with and without accompanying degeneration, and wide distribution of bizarrely shaped pleomorphic nuclei (figs 10 and 11) present in both the ventricular and atrial myocardium. Both the fibrotic degeneration and the bizarre pleomorphic nuclei were em-

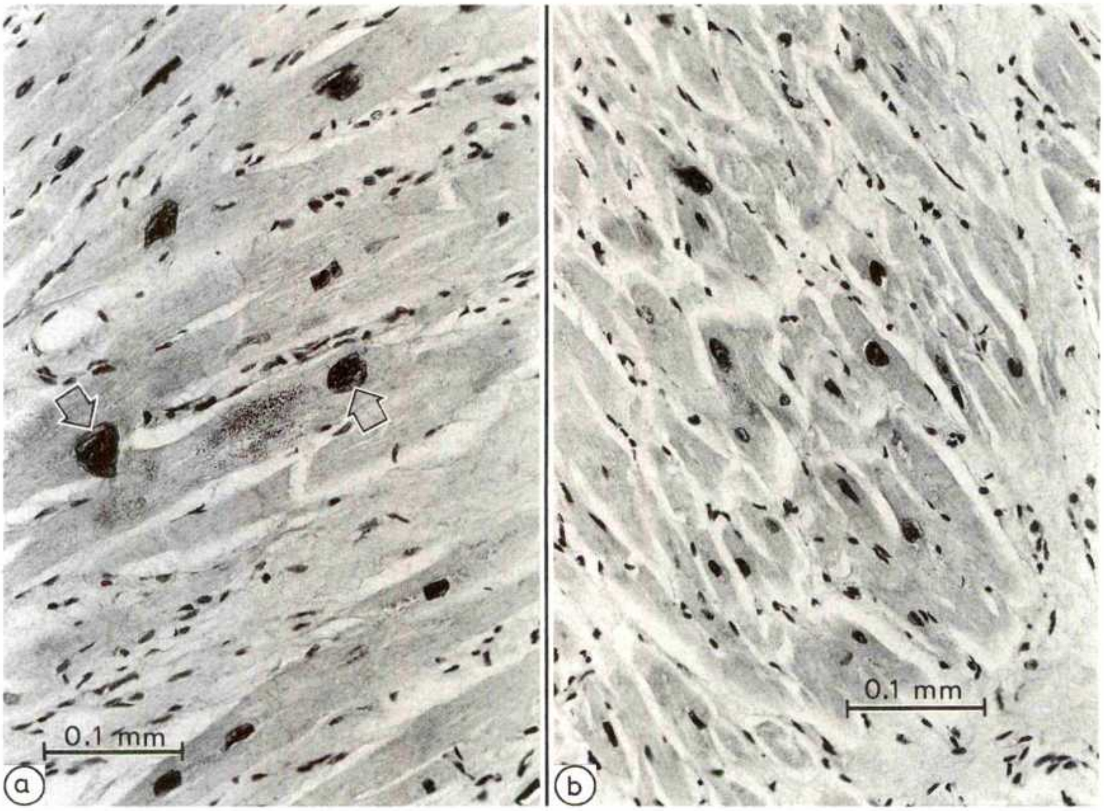

Fig 10 *Photomicrographs showing pleomorphic myocardial nuclei (two indicated with open arrows in (a)) in the interventricular septum near the atrioventricular node. Periodic acid-Schiff stain.*

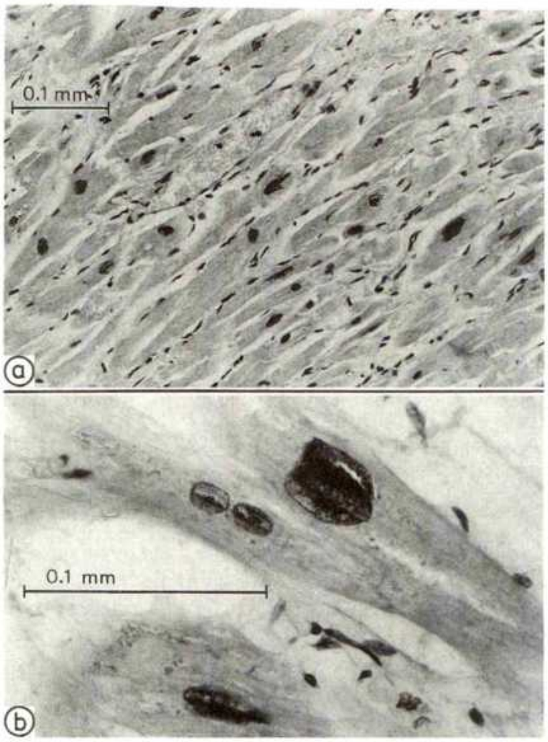

Fig 11 *Photomicrographs showing other pleomorphic nuclei from the same region as in fig 10. Note the giant nucleus in (b). Periodic acid-Schiff stain.*

phasised by Russell.[5] Although she referred to these features collectively as myocarditis, the implication for some workers (though not her, of course) that an infection was somehow involved suggests that it would be better to use some other term. The non-committal and non-specific term, cardiomyopathy, seems suitable, with special emphasis upon the unusual nuclear features in these cases (figs 10 and 11).

As with the cardioneuropathy, there was no consistent spatial relation between observed neural or arterial lesions and those of the myocardium. There can be little doubt, however, that some and possibly much of the focal myocardial degeneration was causally related and attributable to some of the focal arterial lesions that severely narrowed or obliterated those arteries. An assessment of the functional significance of the cardioneuropathy is complicated by the fact that neural abnormalities in the extracardiac nerves or the spinal cord or brain could also have profound effects upon the myocardium.

Discussion

The findings in these three cases, the clinical features of which are representative of most reported experiences with Friedreich's cardiomyopathy, lead to a reasonable multicomponent concept of the pathogenesis of the disease. These components include disease of both the large and small coronary arteries but especially the small ones, cardioneuropathy (nerves and ganglia), and cardiomyopathy (focal fibrosis plus intracellular, especially nuclear, abnormalities of myocytes). In the conduction system these three components could combine to produce the cardiac electrical instability found in Friedreich's ataxia. These components suggest why the heart becomes enlarged and eventually fails, why arrhythmias and conduction disturbances are so common, and why there is often an inexorably downhill clinical course with death within the first two or three decades.

CORONARY DISEASE

For many years coronary disease has been suspected in patients with Friedreich's ataxia for some obvious reasons. They often complain of chest pains. Their electrocardiograms often show widespread inversion of T waves. They often have palpitation, arrhythmias, syncope, and sudden death. None the less, there is not simply a continuing dispute as to the importance of coronary disease in Friedreich's cardiomyopathy—most reports and reviews of the subject dismiss the coronary lesions as not functionally significant, largely on the basis of Hewer's interpretations.[11] The occurrence of lesions in the small coronary arteries, which Hewer and many others have now documented, is not disputed.[5 6 8–10 12] Two factors will help clarify this matter: they are an examination of the history of such studies and a specific critique of the Hewer study.

Although she did not emphasise the finding, Russell found atheroma in two of her four cases and she commented that in one (her case 3) both the large coronary arteries and their branches were constricted but not occluded.[5] Whether these lesions were caused by atheroma or some other narrowing process is uncertain. Their occurrence in such young individuals (in her cases ages 12 and 21 years), however, makes one suspect some non-atheromatous process. In describing Russell's studies Hewer wrote that she "does not mention any microscopical abnormality of the cardiac vessels". This is not true. The next major contribution was that of Nadas and his colleagues who first illustrated unequivocal lesions of coronary arteries, which they interpreted cautiously but correctly.[6] Unfortunately, they did not make it clear that the reported lesions were in the small rather than the large coronary arteries—we have confirmed this finding in the samples that they allowed us to study.

Because of the Nadas report and in view of the widely recognised electrocardiographic abnormalities, interpreted by some as representing myocardial ischaemia and even infarction, Boyer *et al* studied 33 cases of Friedreich's cardiomyopathy for which there was necropsy information on two of the eight that died.[7] It was clear from their report that they were seeking large coronary lesions of the type often associated with conventional myocardial infarction, and they found coronary atherosclerosis "without lumen occlusion" in one of the two necropsy cases, a 25 year old woman. Based upon clinical evidence, mainly electrocardiograms (there were no coronary arteriograms), they concluded that coronary disease was not the basis of Friedreich's cardiomyopathy. But they did not examine the small coronary arteries in the two necropsy cases, or at least they did not report that they had. Since then the clinical importance of coronary spasm has come to be widely accepted, including its occurrence in Friedreich's cardiomyopathy.[29] Thus it is possible that some of the "insignificant" lesions in the large coronary arteries may have been erroneously dismissed.

The study reported by Hewer in 1969 is often cited as providing the definitive answer.[11] From a review of 27 cases he concluded that lesions causing narrowing of the small coronary arteries were indeed present but "that the vast majority of cardiac arteries are not obviously narrowed"; this is a misinterpretation of his own findings to which we will return. He further concluded that the coronary narrowing that he did find was secondary to involution of cardiac muscle, although little evidence is presented to support this interpretation. If he examined any of his sections with the periodic acid-Schiff stain, for example, he does not report it. He does not explain how this unusual and perhaps unique lesion in Friedreich's cardiomyopathy could be secondary to involution of cardiac muscle or how such a process could lead to focal fibromuscular dysplasia or other structural lesions. It is at least as plausible to interpret involution of muscle as being due to coronary disease as the reverse.

But the conduct of the Hewer study itself is more fundamentally flawed. Most subsequent reviewers describing the cardiomyopathy of Friedreich's ataxia refer to his 27 cases, but Hewer was able to examine tissue from only 16 of these cases. Neither the amount or nature of the tissue or its source in the heart is described for these 16 cases and it is uncertain whether he had one slide or more, whether wet tissue was included for special staining, whether the sample came from representative areas of any given cardiac chamber, or how well preserved and suitable for any sort of study some of these archival samples were. He had three (not the often quoted 27) whole hearts to examine, and he made bread loaf slices of them to obtain a large segment of myocardium from which to do his 100 count examinations. Conventional ventricular sections prepared with cuts perpendicular to the epicardium are suitable for examinations of right ventricular or atrial coronary arteries, where most of the small branches run parallel to the epicardium, but not for the left ventricle or interventricular septum where such cuts would lie parallel to the major course of most small coronary arteries.[35] Though this limited Hewer's sampling opportunity, his subsequent count of 100 consecutively encountered cross sections of arteries does provide the data he sought although it may not be representative of all regions of the heart.

His use of the 100 count approach was then encumbered by the arbitrary criterion that a narrowing was regarded as functionally significant only if >50% of the lumen was affected. This makes no allowance for postmortem shrinkage of hearts in which the vessels were not fixed in distension (which would have led to an overestimate of lesions) nor for the possible importance of spasm in diseased arteries with <50% narrowing (which would underestimate significance). Most of the coronary branches that regulate flow are of the size being considered (100 to 1000 μm in diameter) and observed abnormalities of their walls cannot be dismissed simply because they do not cause 50% narrowing of the lumen at necropsy.

Small arteries of the heart are not simply passive conduits. To regulate coronary flow they must not only have an adequate lumen but they must also be capable of responding appropriately to neurohormonal signals for dilatation or constriction as metabolic and functional needs require. Structural disease of such vessels may be expected to distort significantly their responses to either neural or hormonal influences, so that they would be unable to dilate or to constrict when they should. Some of the examples we report here (figs 3–6) as well as figs 7 to 9 in Hewer's own study could hardly be expected to behave in a physiological manner, whatever the degree of luminal narrowing may have been.

The most serious error in the Hewer study is his interpretation that 91% of arteries were normal, or conversely that only 9% had significantly narrowed lumens. His data do not represent arteries per se, but only cross sections of arteries. What he observed was that 9% of such cross sections were significantly narrowed, which tells us about only a thin section of a comparatively long artery. In the human left ventricle such arteries are regularly 20 to 30 mm long, and in the interventricular septum they are often longer.[36] The sinus node artery is frequently 50 to 100 mm long in the normal adult human heart.[37] A study with 8 μm sections to assess the patency of such arteries would require several thousand sections per artery. Even with Hewer's 30 μm slices one would need over one thousand sections to assess the patency of such arteries.

An obstructing lesion (50% or even 100% occlusion) need not be very long, but it would eliminate all distal flow in that vessel. If such a lesion were 100 μm long (some of the pronounced narrowings we observed in serial sections were shorter than that), an observer would have only one chance in several hundred sections of a 30 or 40 mm (30 000 to 40 000 μm) artery of finding such a lesion; Hewer reported that he found lesions in 9% of the arteries that he examined. This is at least several times more than would be expected by chance alone. We do not dispute the accuracy of his observations which we were able to confirm, but his interpretation is wrong. Hewer in essence made a two dimensional analysis of a three dimensional problem.

In addition to the significant lesions in small coronary arteries we should probably reconsider the findings in the large coronary arteries. Several previous observers have found "atheroma" of major coronary arteries but have regarded them as not clinically significant because the lumen was not obstructed (sic).[5 7 8] We can no longer think of larger coronary arteries as simply passive conduits either. Not only is spasm of the large coronary arteries an accepted clinical entity but it has been found in a patient with Friedreich's cardiomyopathy.[29] Thus the entire coronary tree must be suspect in the pathogenesis of heart disease in patients with Friedreich's cardiomyopathy.

CARDIONEUROPATHY

To our knowledge this is the first study of abnormalities of the nerves and ganglia of the heart in Friedreich's ataxia. Extracardiac neural abnormalities (not studied here) may also contribute to disturbances of cardiac rhythm or conduction or repolarisation, as well as contractility and coronary tone. They apparently are responsible for labile hypertension in some patients with Friedreich's ataxia.[26]

One of the most familiar clinical features of Friedreich's cardiomyopathy is widespread inversion of T waves in the electrocardiogram. Possible explanations must include the known focal degeneration and fibrosis in the myocardium, some but certainly not all of which may be related to disease of the small coronary arteries. Another explanation, however, may be neural disease both within and outside the heart. Neural control of the heart profoundly influences almost every component of its function, but it is especially effective upon the processes governing repolarisation and thus the appearance of the ST segment and T wave.[38]

Cardioneuropathy may also affect myocardial contractility. The inevitable regional variations in the neural inotropic influence may be the basis of some of the unusual changes in segmental wall motion or other ventricular contractile abnormalities described in Friedreich's cardiomyopathy [13–16 20 27–29]

CARDIOMYOPATHY

There is not much dispute about the general nature of the myocardial lesions: hypertrophy of fibres, widely scattered focal degeneration and varying degrees of fibrosis, and the unusual nuclear abnormalities first described by Russell. Hypertrophy of the heart is generalised, as are each of the myocardial lesions. Hypertrophy is sometimes asymmetrical[13–15]; but this is the exception rather than the rule. As discussed previously,[8] it seems reasonable to attribute some of the focal degeneration and fibrosis in the myocardium to narrowing lesions of the small coronary arteries. The association with focal lesions in the sinus node that we saw in all three of the present cases coupled with focal pronounced narrowing of branches of the sinus node artery is particularly persuasive since all three patients had documented atrial arrhythmias. Neither the pathogenesis nor the functional significance of the bizarre pleomorphic nuclei is apparent.

A MOSAIC CONCEPT OF PATHOGENESIS

The indisputable lesions of both the small and large coronary arteries, the demonstrable abnormalities of the nerves and ganglia, and the changes seen in the myocytes are three components in a mosaic concept of the pathogenesis of Friedreich's cardiomyopathy (fig 12). All three abnormalities probably have some influence on each other. For example, sufficient narrowing of the arteries—whether by a visualised structural lesion or by intermittent spasm—can cause focal ischaemia not only of myocytes but also of nerves and ganglia. Such focal neural ischaemia may distort responses by the heart to extracardiac neural influence generated either by intermittent

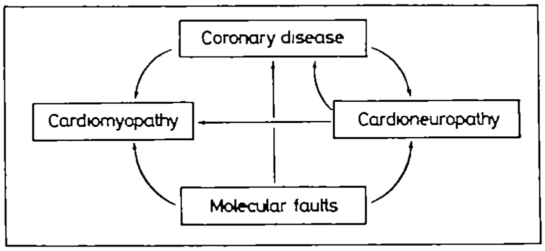

Fig 12 *The multifactorial nature of abnormalities in Friedreich's cardiomyopathy*

reflexes or by more sustained disease of the type intrinsic to Friedreich's ataxia. Neural injury may also be the source of either excitatory[39] or depressive[40] cardiogenic reflexes. For example, labile hypertension observed in Friendreich's ataxia[27] could have its origin within the heart.[39] From a general assessment of the areas of focal degeneration and fibrosis of myocardium it seems unlikely that these can be entirely attributed to the arterial lesions, but some must be. Further studies in vivo, such as thallium scans and assessment of coronary reserve, are needed to determine how much of the myocardial abnormality is the result of ischaemia, which is largely attributable to the functional behaviour of the small coronary arteries.[41-49]

In one study of 14 patients with Friedreich's cardiomyopathy thallium scans showed abnormal myocardial perfusion in every case.[27] Although the workers did not interpret their findings as being caused by abnormal coronary flow, claiming that in their own experience the large and small coronary arteries did not show "significant atherosclerotic involvement", their previous morphological study actually demonstrated mild to moderate disease of the small coronary arteries in each of their three cases.[12] Therriault *et al* offer no convincing alternative explanation,[27] but we agree with others[42 43 47-49] that the most logical cause of functional abnormalities in such thallium scans is abnormal small coronary arteries.

Hypertrophy and myocytopathy of the heart in Friedreich's ataxia can also partially be attributed to a compensatory response to recurring focal ischaemia, but the prevalence of bizarre nuclei within the myocytes suggests some more fundamental fault, perhaps in intracellular metabolism. Whether the cardioneuropathy contributes to myocardial hypertrophy depends upon several factors. If the nerves affected are of sympathetic origin then during any excitatory phase of the disease they may release sufficient local noradrenaline to produce hypertrophy.[50 51] Later, when the nerves may be destroyed or inactive, the focal loss of a positive inotropic influence may lead to abnormal local stress which could end in compensatory hypertrophy. Overactivity of local nerve endings could even lead to fibromuscular dysplasia of the small or large coronary arteries, as was suggested for the myocardium. If such focal fibromuscular dysplasia has its origin in some non-neural process it may nevertheless make the local area supplied by the affected artery over responsive to either normal or increased neural influence.

All three of these pathogenetic components converge in the cardiac conduction system and particularly the sinus node. There one finds abnormally narrowed arteries, degenerated nerves and ganglia, and pleomorphic nuclei in abundance. Since atrial arrhythmias are common in patients with Friedreich's cardiomyopathy (all three of our cases), this added physiological stress brought about by disease within the conduction system could even be considered a fourth component in the pathogenesis of Friedreich's cardiomyopathy.

Only by concomitantly considering all of the arterial, neural, and myocardial facets of this complex disease can any reasonable synthesis be made of the pathogenesis of Friedreich's cardiomyopathy. In different cases the individual contributions of these components will undoubtedly vary both in size and timing. Ultimately, of course, we must seek further for the various postulated molecular faults which may be responsible,[17 21-24] but it is perplexing how a single or closely related group of such molecular faults could account for such diverse components in this pathogenesis. If there is a common thread, as indeed there may be, it is not yet apparent.

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References

1 Friedreich N. Ueber degenerative atrophie der spinalen hinterstrange. *Arch Path Anat Physiol Klin Med* 1863;27:1–26.

2 Pentland B, Fox KAA. The heart in Friedreich's ataxia. *J Neurol Neurosurg Psychiatry* 1983;46:1138–42.

3 Child JS, Perloff JK, Bach PM, *et al.* Cardiac involvement in Friedreich's ataxia: a clinical study of 75 patients. *J Am Coll Cardiol* 1986;7.1370–8.

4 Laubry C, Heim de Balsac R. A propos des troubles cardiaques de la maladie de Freidreich. *Bull Soc Med Hop Paris* 1936;52:756–9.

5 Russell DS. Myocarditis in Friedreich's ataxia. *J Pathol Bacteriol* 1946;58·739–48.

6 Nadas AS, Alimurung MM, Sieracki LA. Cardiac manifestations of Friedreich's ataxia. *N Engl J Med* 1951;244:239–44.

7 Boyer SH, Chisholm AW, McKusick VA. Cardiac aspects of Friedreich's ataxia. *Circulation* 1962; 25.493–505.

8 James TN, Fisch C. Observations on the cardiovascular involvement in Friedreich's ataxia. *Am Heart J* 1963;66:164–75.

9 Ivemark B, Thoren C. The pathology of the heart in Friedreich's ataxia. Changes in coronary arteries and myocardium. *Acta Med Scand* 1964;175:227–37

10 Varnauskas E, Ivemark B, Paulin S, Ryden B Obscure cardiomyopathies with coronary artery changes. *Am J Cardiol* 1967;19:531–41.

11 Hewer RL. The heart in Friedreich's ataxia. *Br Heart J* 1969;31:5–14

12 Lamarche JB, Cote M, Lemieux B. The cardiomyopathy of Friedreich's ataxia. morphological observations in 3 cases. *Can J Neurol Sci* 1980;**7**:389–96.

13 Gach JV, Andriange M, Franck G. Hypertrophic obstructive cardiomyopathy and Friedreich's ataxia. *Am J Cardiol* 1971;**27**:436–41.

14 Boehm TM, Dickerson RB, Glasser SP. Hypertrophic subaortic stenosis occurring in a patient with Friedreich's ataxia. *Am J Med Sci* 1971;**260**:279–84.

15 Ruschhaupt DG, Thilenius OG, Cassels DE. Friedreich's ataxia associated with idiopathic hypertrophic subaortic stenosis. *Am Heart J* 1972; **84**:95–102.

16 Van der Hauwaert LG, Dumoulin M. Hypertrophic cardiomyopathy in Friedreich's ataxia. *Br Heart J* 1976;**38**:1291–8

17 Blass JP, Kark RAP, Menon NK. Low activities of the pyruvate and oxoglutarate dehydrogenase complexes in five patients with Friedreich's ataxia. *N Engl J Med* 1976;**295**:62–7.

18 O'Brien ET, Dajee H, Ward OC. Friedreich's disease—a family study. *Eur J Cardiol* 1977;**6**:15–24.

19 Cote M, Bureau M, Leger C, *et al.* Evolution of cardiopulmonary involvement in Friedreich's ataxia. *Can J Neurol Sci* 1979;**6**:151–7.

20 Berg RA, Kaplan AM, Jarrett PB, Molthan ME. Friedreich's ataxia with acute cardiomyopathy. *Am J Dis Child* 1980;**134**:390–3.

21 Barbeau A. Friedreich's ataxia 1980. An overview of the physiopathology. *Can J Neurol Sci* 1980;**7**:455–68.

22 Gottdiener JS, Hawley RJ, Maron BJ, Bertorini TF, Engle WK. Characteristics of the cardiac hypertrophy in Friedreich's ataxia. *Am Heart J* 1982;**103**:525–31.

23 Stumpf DA. Friedreich's disease: a metabolic cardiomyopathy. *Am Heart J* 1982;**104**:887–8.

24 Pasternac A, Wagniart P, Olivenstein R, *et al.* Increased plasma catecholamines in patients with Friedreich's ataxia. *Can J Neurol Sci* 1982;**9**:195–203.

25 Harding AE, Hewer RL. The heart disease of Friedreich's ataxia: a clinical and electrocardiographic study of 115 patients, with an analysis of serial electrocardiographic changes in 30 cases. *Q J Med* 1983;**52**:489–502.

26 Margalith D, Dunn HG, Carter JE, Wright JM. Friedreich's ataxia with dysautonomia and labile hypertension. *Can J Neurol Sci* 1984;**11**:73–7.

27 Theriault L, Lamoureux G, Cote M, Plourde G, Lemieux B. Cardiomyopathy in Friedreich's ataxia: ventriculography and myocardial imaging with thallium-201. *Can J Neurol Sci* 1984;**11**:588–91.

28 Steinsapir K, Lewis W. Dilated cardiomyopathy associated with Friedreich's ataxia. *Arch Pathol Lab Med* 1985;**109**:454–6.

29 Sohi GS, Drake C, Flowers NC. Friedreich's ataxia associated with hypertrophic cardiomyopathy and coronary vasospasm. *Clin Cardiol* 1985;**8**:537–41.

30 Hawley RJ, Gottdiener JS. Five-year follow-up of Friedreich's ataxia cardiomyopathy. *Arch Intern Med* 1986;**146**:483–8.

31 Casazza F, Ferrari F, Finocchiaro G, *et al.* Echocardiographic evaluation of verapamil in Friedreich's ataxia. *Br Heart J* 1986;**55**:400–4.

32 James TN. The sinus node. *Am J Cardiol* 1977;**40**:965–86.

33 James TN. Structure and function of the AV junction. The Mikamo Lecture for 1982. *Jpn Circ J* 1983;**47**:1–47.

34 James TN. Primary and secondary cardioneuropathies and their functional significance. *J Am Coll Cardiol* 1983;**2**:983–1002.

35 James TN. Small arteries of the heart. The 36th George E Brown Memorial Lecture. *Circulation* 1977;**56**:2–14.

36 James TN, Burch GE. Blood supply of the human interventricular septum. *Circulation* 1958;**17**:391–6.

37 James TN. *Anatomy of the coronary arteries.* Hagerstown, Maryland: Harper and Row, 1961.

38 Abildskov JA. Adrenergic effects on the QT interval of the electrocardiogram. *Am Heart J* 1976;**92**:210–6.

39 James TN, Isobe JH, Urthaler F. Analysis of components in a hypertensive cardiogenic chemoreflex. *Circulation* 1975;**52**:179–92.

40 Frink RJ, James TH. The intracardiac route of the von Bezold-Jarisch reflex. *Am J Physiol* 1971;**221**:1464–9.

41 Strauer BE. Die quantitative bestimmung der koronarreserve zur diagnostik koronarer durchblutungsstorungen. *Der Internist* 1977;**18**:579–87.

42 Factor SM, Minase T, Cho S, Dominitz R, Sonnenblick EH. Microvascular spasm in the cardiomyopathic Syrian hamster; a preventable cause of focal myocardial necrosis. *Circulation* 1982;**66**: 342–54.

43 Cannon RO III, Watson RM, Rosing DR, Epstein SE. Angina caused by reduced vasodilator reserve of the small coronary arteries. *J Am Coll Cardiol* 1983;**1**:1359–73.

44 Opherk D, Mall G, Zebe H, *et al.* Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. *Circulation* 1984;**69**:1–7.

45 Strauer BE. The coronary circulation in hypertensive heart disease. *Hypertension* 1984;**6** (suppl III).74–80.

46 Cannon RO III, Watson RM, Rosing DR, Epstein SE Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve *Am J Cardiol* 1985;**56**:242–6.

47 Kahan A, Nitenberg A, Foult J-M, *et al.* Decreased coronary reserve in primary scleroderma myocardial disease. *Arthritis Rheum* 1985;**28**:637–46.

48 Legrand V, Mancini GBJ, Bates ER, Vogel RA. Evidence of abnormal vasodilator reserve in coronary spasm. *Am J Cardiol* 1986;**57**:481–2.

49 Kimball BP, Shurvell BL, Mildenberger RR, Houle S, McLaughlin PR. Abnormal thallium kinetics in postoperative coarctation of the aorta: evidence for diffuse hypertension-induced vascular pathology. *J Am Coll Cardiol* 1986;**7**:538–45.

50 Laks MM, Morady F, Swan HJC. Myocardial hypertrophy produced by chronic infusion of subhypertensive doses of norepinephrine in the dog. *Chest* 1973;**64**:75–8.

51 Simpson P. Stimulation of hypertrophy of cultured neonatal rat heart cells through an α_1-adrenergic receptor and induction of beating through an α_1-and β_1-adrenergic receptor interaction. *Circ Res* 1985;**56**:884–94.

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Suppressor T lymphocyte function in patients with idiopathic congestive cardiomyopathy

PATRICIA J LOWRY, M D GAMMAGE, TRUDIE A GENTLE,* MARGARET I D BAYNHAM,* R A THOMPSON,* W A LITTLER

From the Departments of Cardiovascular Medicine and Immunology, University of Birmingham and East Birmingham Hospital, Bordesley Green East, Birmingham*

SUMMARY Suppressor T lymphocyte function was examined in 11 patients with idiopathic congestive cardiomyopathy and in 11 age and sex matched patients with a similar degree of heart failure resulting from ischaemic heart disease. Suppressor T lymphocyte function was also assessed in a control population of 11 normal subjects. Suppressor T lymphocyte function was reduced in both groups of patients with heart failure but not significantly, and a wide range of suppression was demonstrated in all groups.

These data do not support the hypothesis that there is a defect in T lymphocyte function in patients with congestive cardiomyopathy, but they do suggest that there may be a non-specific reduction in T lymphocyte suppressor function associated with heart failure in general.

The aetiology of idiopathic congestive cardiomyopathy is, by definition, unknown and is likely to represent the end stage of several different pathogenic mechanisms.[1 2] The possibility that immunological abnormalities may affect the pathogenesis of some cases has received much attention in recent years.[3 4] There have been reports of impaired suppressor T lymphocyte function in patients with congestive cardiomyopathy and this could be the result of a quantitative or a qualitative abnormality.[5 6] Such a defect might be determined genetically by predisposing an individual to viral infection, myocarditis, and subsequent development of cardiomyopathy.[7] This hypothesis has not, however, been accepted by all workers[8] and some studies have shown no specific abnormality of T lymphocyte function in congestive cardiomyopathy.[9]

These doubts regarding the role of immunological abnormalities in the pathogenesis of congestive cardiomyopathy prompted a study to determine whether patients with congestive cardiomyopathy have a defect of suppressor T lymphocyte function that is specific to their disease.

Patients and methods

PATIENTS

Eleven patients with idiopathic congestive cardiomyopathy (according to the classification of Goodwin and Oakley)[1] that was confirmed by cardiac catheterisation, coronary angiography, and left ventricular endomyocardial biopsy were studied and compared with eleven individually age and sex matched patients who had congestive cardiac failure of ischaemic origin, also confirmed at cardiac catheterisation. We also studied eleven healthy controls recruited from hospital staff with no personal or family history of ischaemic heart disease.

The severity of congestive cardiac failure and the treatment regimens were similar in the patient groups (table). All patients in the heart failure groups were being treated with digoxin and warfarin. Ejection fractions were determined by volumes derived from end systolic and end diastolic frames acquired at left ventricular cineangiography.[10]

METHODS

Lymphocytes were separated from heparinised blood by density gradient centrifugation.[11] Suppressor activity was induced by culturing cells with concanavalin A (con A) at two concentrations—30

Requests for reprints to Dr Patricia J Lowry, Department of Cardiovascular Medicine, East Birmingham Hospital, Bordesley Green East, Birmingham B9 5ST.

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Table *Data on the groups of patients and controls that were studied*

	Congestive cardiomyopathy	*Ischaemic heart disease*	*Healthy controls*
Age (yr) (mean (SD))	47 (13)	52 (10)	44 (16)
Ejection fraction (mean (SD))	0·32 (0·12)	0·29 (0·12)	—
Average daily dose of frusemide (mg)	69 (range 40–120)	73 (range 40–120)	— —
Number of patients taking vasodilators	7	8	—
Number of subjects	11	11	11

and 10 µg/ml—and incubating them for 48 hours at 37°C in a humidified atmosphere containing 5% carbon dioxide. Parallel cultures in medium alone provided the control cells. The cell division of suppressor cells was inhibited by treatment with mitomycin C (2·5 µg/10^6 lymphocytes). Three normal healthy adults (responders 1, 2, and 3) were used as the source of responder cells. Lymphocytes from responders were incubated with suppressor cells in medium alone or with phytohaemagglutinin (PHA) 25 µg/ml in ratios of suppressor to responders of 2:1 and 1:1. Cultures were incubated in triplicate for three days at 37°C in a humidified atmosphere containing 5% carbon dioxide. Sixteen hours before harvesting 0·6 µCi of [^{3}H]thymidine was added to each culture and uptake of label was measured as disintegrations/minute (dpm) in a scintillation counter. Percentage suppression was calculated by the formula:

$$100 \times \left[1 - \frac{\text{dpm responder cells + PHA + con A treated cells}}{\text{dpm responder cells + PHA + control cells}}\right]$$

where dpm = mean uptake by stimulated cultures minus mean uptake by unstimulated cultures.

STATISTICAL ANALYSIS

Analysis of variance was used to assess the statistical significance of differences between the groups; $p < 0·05$ was taken to indicate statistical significance.

Results

There was a wide variation in the percentage inhibition produced by suppressor cells tested with cells from different responders. This variation was most pronounced in both patient groups (fig 1).

Figure 2 shows the wide range of suppression in all groups; this was more pronounced in the patient groups. Initial experiments indicated that for optimum reproducibility suppressor cells should be induced with concanavalin A; however, use of different concentrations of concanavalin A (30 and 10 µg/ml) made no difference to the range of sup-

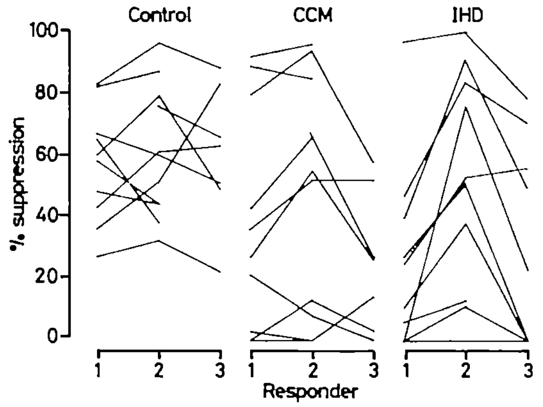

Fig 1 *Percentage suppression produced by 30 µg/ml concanavalin A at a ratio of suppressor to responder cells of 2:1 with each of the three responders. CCM, congestive cardiomyopathy; IHD, ischaemic heart disease.*

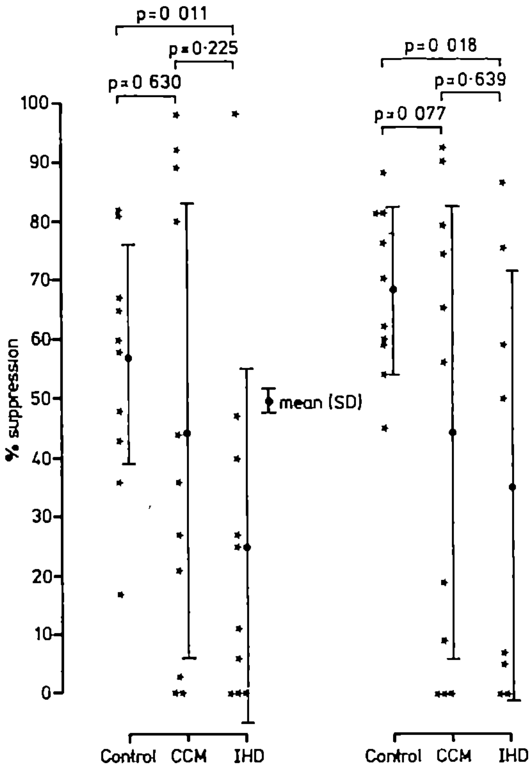

Fig 2 *Percentage suppression produced by (a) 30 µg/ml concanavalin A and (b) 10 µg/ml concanavalin A at a ratio of suppressor to responder cells of 2:1 (responder 1). CCM, congestive cardiomyopathy; IHD, ischaemic heart disease.*

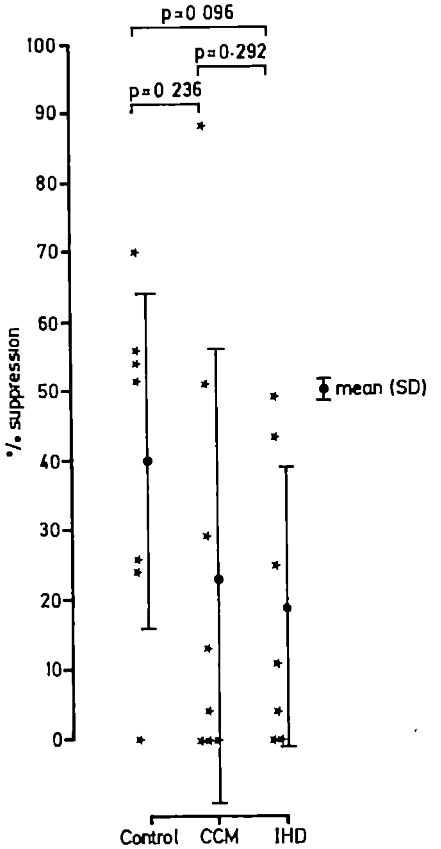

Fig 3 *Percentage suppression produced by 30 μg/ml concanavalin A at a ratio of suppressor to responder cells of 1:1 (responder 1). CCM, congestive cardiomyopathy; IHD, ischaemic heart disease.*

pression seen. There were no significant group differences between the controls and patients with congestive cardiomyopathy (p = 0·63 at 30 μg/ml; p = 0·08 at 10 μg/ml) or between patients with congestive cardiomyopathy and ischaemic heart disease (p = 0·23 at 30 μg/ml; p = 0·64 at 10 μg/ml), but there was a significant difference between controls and patients with ischaemic heart disease at both concanavalin A concentrations (p = 0·01 at 30 μg/ml; p = 0·02 at 10 μg/ml).

When different responders were used we also found the same trend towards lower mean suppression in the heart failure groups with no significant difference between those with congestive cardiomyopathy and those with ischaemic heart disease. Use of a cell ratio of suppressor to responder of 1:1 rather than 2:1 also resulted in a wide range of suppression within each group; again this was more pronounced in the two patient groups (fig 3). At this ratio (1:1) there were no significant differences between any of the groups.

Discussion

Abnormalities of cellular immunity are known to occur in heart diseases such as rheumatic fever,[12] Chagas's disease,[13] and even in association with ischaemic heart disease.[14] Whether these abnormalities are pathogenic, however, remains unclear. It has been suggested that the normal cell mediated immunological process is in some way deficient in congestive cardiomyopathy[3 15]; attention has been directed towards the immunoregulatory function of T lymphocytes and a quantitative or qualitative abnormality of the ratio of helper to suppressor T lymphocytes has been suggested.[5-7] Suppressor T lymphocytes regulate helper T lymphocytes and thereby influence antibody production and cell mediated immunity.[16] Failure of suppression by suppressor T lymphocytes has been demonstrated[6] in patients with congestive cardiomyopathy but not in patients with ischaemic heart disease.[5] This finding has led to the hypothesis that B lymphocyte activity, autoantibody formation, and cell mediated immunity may be abnormal in patients with congestive cardiomyopathy.[7] A report that lymphoma developed in six of 37 patients who had cardiac transplants because of congestive cardiomyopathy in contrast with none of 54 patients who had cardiac transplants because of ischaemic heart disease was believed to add weight to the suggestion that impaired suppressor T lymphocyte function was of aetiological importance in congestive cardiomyopathy.[17] A deficiency of suppressor activity was demonstrated in only one of the six patients with lymphoma, however.

We found a statistically non-significant trend for suppression in patients with congestive cardiomyopathy to be lower than in normal controls; there was a similar trend in patients with ischaemic heart disease when compared with controls, which reached statistical significance on two occasions (at concanavalin A concentrations of 10 and 30 μg/ml with cell ratio of suppressor to responder of 2:1) but with only one of the three responders. No statistically significant difference in percentage suppression was demonstrated between congestive cardiomyopathy and ischaemic heart disease at either concentration or ratio. No significant abnormality of suppressor T lymphocyte function was found in congestive cardiomyopathy and the trend towards lower suppression in patient groups suggests a nonspecific abnormality related to illness. Other studies have failed to confirm an abnormality of suppressor T lymphocyte function specific to congestive cardiomyopathy[9 18] or ischaemic heart disease.[5] Low suppressor T lymphocyte activity has been demonstrated, however, in myocarditis.[6] Does this represent a primary immunological defect responsible wholly or in part for pathogenesis or does it merely reflect a secondary phenomenon of heart disease? The possibility that medication or chronic illness per se may affect T lymphocyte function must be considered; this may account for the similarity in results between the two patient groups in this study with a reduction in suppression in both groups.

Immunological response, including suppressor T lymphocyte function, changes with age.[19] The mean ages of study groups are therefore important and sometimes are not given in published reports.[6] Even in a study in which low suppressor activity has been demonstrated in a group of patients with congestive cardiomyopathy, normal individual controls may show variation in suppression from 0% to 100%.[6] Shou *et al* demonstrated important variation between individuals and in some cases they were unable to demonstrate suppressor activity at all.[20] Use of different responder cells in this study has highlighted this variability even in normal subjects. A study of change in suppressor T lymphocyte activity with time in patients with congestive cardiomyopathy, other heart diseases, and normal controls may clarify the role of suppressor T lymphocyte function and the variability in results of reported studies.

The ratio of suppressor to responder cells is also important—the greater the ratio the better—as is the length of incubation period during generation of suppressor cells.[19] Initial experiments in our laboratory indicated that optimum reproducibility occurred with induction of suppressor cells with concanavalin A and stimulation of responder cells by phytohaemagglutinin.

Using this assay we have not been able to demonstrate an innate suppressor T lymphocyte defect which is specific to congestive cardiomyopathy. Poor cardiac function (resulting from either cardiomyopathy or myocardial ischaemia), however, may be associated with abnormalities of suppressor T cell function.

References

1 Goodwin JF, Oakley CM. The cardiomyopathies. *Br Heart J* 1972;34:545–52.

2 Goodwin JF. Cardiomyopathy: an interface between fundamental and clinical cardiology. In: Hayase S, Murao S, eds. *Cardiology*. (International Congress Series No. 470.) Amsterdam: Excerpta Medica, 1979:102–16.

3 Das SK, Petty RE, Meengs WA, Tubergen DG. Studies of cell-mediated immunity in cardiomyopathy. In: Sekiguchi M, Olsen EGJ, eds. *Cardiomyopathy*. Tokyo: University of Tokyo Press, and Baltimore: University Park Press, 1980:375–9.

4 Das SK, Stein LD, Reynolds RT, Thebert P, Cassidy JT. Immunologic studies in cardiomyopathy and pathophysiologic implications. In: Goodwin JF, Hjalmarson A, Olsen EJG, eds. *Congestive cardiomyopathy*. Molndal, Sweden: AB Hassle, 1981: 87–93.

5 Fowles RE, Bieber CP, Stinson EB. Defective in vitro suppressor cell function in idiopathic congestive cardiomyopathy. *Circulation* 1979;59:483–91.

6 Eckstein R, Mempel W, Bolte H-D. Reduced suppressor cell activity in congestive cardiomyopathy and in myocarditis. *Circulation* 1982;65:1224–9.

7 Bolte H-D. Dilated (congestive) cardiomyopathy—arguments for immunological relevance. In: Goodwin JF, ed. *Heart muscle disease*. Lancaster, Boston, The Hague, Dordrecht: M.T.P. Press, 1985:273–84.

8 Lowry PJ, Thompson RA, Littler WA. Cellular immunity in congestive cardiomyopathy: the normal cellular immune response. *Br Heart J* 1985;53:394–9.

9 Anderson JL, Greenwood JH, Kawanishi H. Evaluation of suppressor immune regulatory function in idiopathic congestive cardiomyopathy and rheumatic heart disease. *Br Heart J* 1981;46:410–4.

10 Dodge HT, Sandler H, Ballew DW, Lord JD Jr The use of biplane angiocardiography for the measurement of left ventricular volume in man. *Am Heart J* 1960;60:762–7.

11 Boyum A. A one-stage procedure for isolation of granulocytes and lymphocytes from human blood. General sedimentation properties of white blood cells in a 1*g* gravity field. *Scand J Clin Lab Invest* 1968; 21(suppl 97):51–76.

12 Read SE, Fischetti VA, Utermohlen V, Falk RE, Zabriskie JB. Cellular reactivity studies to streptococcal antigens: migration inhibition studies in patients with streptococcal infections and rheumatic fever. *J Clin Invest* 1974;54:439–50.

13 Teixeira ARL, Teixeira G, Macedo V, Prata A. Trypanosome Cruzi-sensitized T-lymphocytes mediated ^{51}Cr release from human heart cells in Chagas' disease. *Am J Trop Med Hyg* 1978;27:1097–107.

14 Wartenberg J, Brostoff J. Leucocyte migration inhibition by heart extract and liver mitochondria in patients with myocardial infarction. *Br Heart J* 1973;35:845–8.

15 Sachs RN, Lanfranchi J. Cardiomyopathies primitives et anomalies immunitaires. *Coeur Méd Intern* 1978;17:193–8.

16 Reinherz EL, Schlossman SF. Regulation of immune response—inducer and suppressor T-lymphocyte subsets in human beings. *N Engl J Med* 1980; 303:370–3.

17 Anderson JL, Fowles RE, Bieber CP, Stinson EB. Idiopathic cardiomyopathy, age and suppressor-cell dysfunction as risk determinants of lymphoma after cardiac transplantation. *Lancet* 1978;ii:1174–6.

18 O'Connell JB, Schervish EW, Kowalczyk D, Robinson JA. Suppressor cell function in idiopathic dilated cardiomyopathy [Abstract]. International Symposium on Inflammatory Heart Disease, 1986:65.

19 Antel JP, Weinrich M, Arnason BGW. Circulating suppressor cells in man as a function of age. *Clin Immunol Immunopathol* 1978;9:134–41.

20 Shou L, Schwartz SA, Good RA. Suppressor cell activity after concanavalin-A treatment of lymphocytes from normal donors. *J Exp Med* 1976;9:1100–10.

Br Heart J 1987;57:462–7

Long term results (15–30 years) of surgical repair of aortic coarctation

P PRESBITERO, D DEMARIE, M VILLANI, E ACTIS PERINETTO, G RIVA, F ORZAN, M BOBBIO, M MOREA, A BRUSCA

From the Istituto di Medicina e Chirurgia Cardiovascolare, Università di Torino, Turin, Italy

SUMMARY The late outcome in 226 patients who survived surgical repair of aortic coarctation was assessed 15–30 years after operation. Twenty six patients died during the follow up mainly from causes related to surgical repair or to associated cardiovascular anomalies. The survival rates of patients operated on between the ages of four and 20 years are 97%, 97%, 92% at 10, 20, and 30 years after operation. For patients operated on after the age of 20 the corresponding rates are 93%, 85%, and 68%. This difference is statistically significant from the fifteenth year of follow up onwards. The survival of patients operated on before the age of 20 is not significantly different from that of a comparable general Italian population. Recoarctation occurred in only 8% of patients who had end to end anastomosis, whereas it occurred in 35% of those who had other types of operation. Two thirds of the patients were hypertensive at the last visit. The actuarial curve shows that blood pressure was normal in most patients 5–10 years after operation, but 30 years after coarctation repair only 32% of patients are expected to be normotensive.

Thus early repair of aortic coarctation appears to improve long term survival. Intervention in older patients and when blood pressure is high seem to be the most important predictors of late hypertension.

Forty years after the first successful operation for the relief of aortic coarctation[1] there is still controversy about the optimal age and the most suitable technique for the repair of this anomaly.[2–4] Long term morbidity and mortality remain high, with complications and deaths being mainly the result of associated cardiovascular lesions, infective endocarditis, and residual or recurrent coarctation and hypertension.[5–7]

We have analysed the long term results of a large group of patients operated on in our institution 15 to 30 years ago.

Patients and methods

PATIENTS

Two hundred and forty four patients (163 male and 81 female) were operated upon from 1954 to 1969 in our department. In all patients the diagnosis had been confirmed by angiography. Two hundred and twenty six patients left the hospital and were followed for 15–30 years (mean 20 years). Resection with end to end anastomosis had been performed in 170 patients; Clagett's operation[8] (end to end anastomosis of the left subclavian artery to the descending aorta) in 25; a prosthetic tube graft had been inserted in 24; and three required a patch repair. Four patients had an operation of another type.

Patients were aged 4–48 years (mean 20) at operation. Their age at last examination ranged from 19 to 65 years (mean 40).

Twenty six patients died and 17 were lost to follow up. Forty patients could be contacted only by telephone. The remaining 143 were assessed in our department.

METHODS

Blood pressure in the arm was measured by a standard sphygmomanometer with a cuff that was 14 cm wide and 48 cm long. Systolic pressure in the legs was measured in either the popliteal artery by means

Requests for reprints to Dr P Presbitero, Istituto di Medicina e Chirurgia Cardiovascolare, Cardiologia I°, Ospedale Molinette, Corso Bramante, 10100 Turin, Italy.

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of a cuff that covered at least two thirds of the thigh or in the posterior tibial artery by a cuff that covered at least two thirds of the calf.

An electrocardiogram and chest *x* ray were obtained in all 143 patients who were reassessed in our department. Twenty patients had left heart catheterisation and angiography because recoarctation or additional cardiovascular anomalies were suspected. Patients aged >30 years were regarded as hypertensive when their systolic blood pressure was >160 mm Hg or the diastolic pressure was >95 mm Hg or both. In those aged between 19 and 30 years hypertension was defined as a systolic pressure of >150 mm Hg or a diastolic pressure of >90 mm Hg or both.[9,10] All patients on antihypertensive treatment were regarded as having hypertension.

Recoarctation was diagnosed when the pressure gradient between arms and legs was >20 mm Hg at rest or >30 mm Hg after exercise.[11,12] Fifteen of the 17 considered to have recoarctation consented to cardiac catheterisation; this confirmed the clinical diagnosis in all except two of the patients who had a gradient of <20 mm Hg.

Standard actuarial methods were used to calculate cumulative incidence rates.[13] Cumulative actuarial curves of survival were constructed for our patients and these were compared with the actuarial survival curves of the Italian population in the years 1967–69. We also compared our results with the survival curves reported by Campbell in patients with coarctation who were not treated by operation.[14]

The actuarial curves of postoperative blood pressure were constructed from the patients' personal medical records and history. Those with recoarctation were excluded. The prevalence of hypertension in our population was compared with that in the Italian population.[15] Hypertension is more common in males than in females and also increases with age. Because the distribution of age and sex in our patients was different from that in the Italian population we have adjusted the crude (observed) hypertension rates of our patients according to the age and sex specific rates of the general Italian population, using the indirect standardisation of rate,[16] to give the expected rates.

We used the χ^2 test to compare the observed and expected data. Between group comparisons were made by the two tailed test of proportion. Differences of $p < 0\cdot05$ were regarded as significant. Data are presented as mean (SEM). Qualitative variables were compared by means of a multifactorial log linear model.[17]

Results

LATE MORTALITY

Twenty six patients died 1–30 years (median 12 years) after the operation at a mean age of 39 years (range 15–53 years). Three patients died of causes related to the surgical repair. Two had had a Clagett's anastomosis; one of them died 16 years after surgery of a ruptured aneurysm of the thoracic aorta and the other died of bleeding at the site of anastomosis after a reoperation 10 years after the first operation. The third patient, in whom a long coarctation had been replaced by a prosthetic tube graft, died of endocarditis a year later.

Seven patients died of coronary heart disease at a mean age of 38 years; four died in cardiac failure because of associated cardiac lesions. Two patients died suddenly. Three patients, two of them with recoarctation, died of a cerebrovascular accident. Two patients died in motoring accidents and in five cases the cause of death is unknown. The mean age at operation was 25 (1·45) years in the patients who died and 19 (0·67) those who survived ($p < 0\cdot02$).

The type of surgical repair seemed to affect late survival. Only 6·3% of the patients who had had end to end anastomosis died, whereas 23% of those who had had other kinds of operation died ($p < 0\cdot01$). In patients aged >20 years at operation, 10% of those who had an end to end anastomosis and 36% of those with other kinds of operation died ($p < 0\cdot05$); thus the type of operation remains an important additional independent risk factor even in patients who were older at operation.

The distribution of age adjusted mortality rate (fig 1) shows that most late deaths after the intervention occurred between the fourth and the fifth decade; in Campbell's study mortality rates reached a peak two decades earlier in patients with coarctation that was not treated by surgical repair.[14]

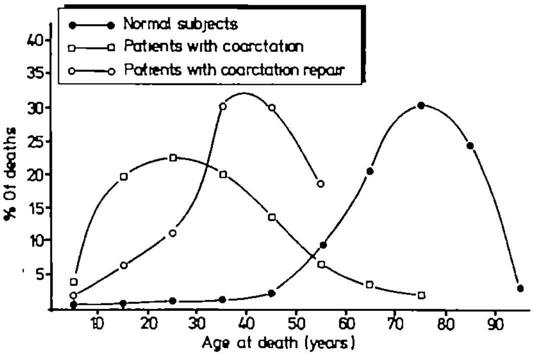

Fig 1 *Distribution of death by age of subjects with coarctation, of subjects with coarctation repair, and of the general population. The curves on the left and right are taken from Campbell.[14] The middle curve shows the distribution of death in our patients with coarctation repair These curves have been adjusted for age.*

SURVIVAL

Thirty years after operation the actuarial survival is 78 (6)% (fig 2). In patients aged 4–20 years at operation survival is 97%, 97%, 92% at 10, 20, and 30 years after operation. For those operated on after the age of 20 the corresponding rates are 93%, 85%, and 68%. The difference between the two curves becomes statistically significant from the fifteenth year of follow up onwards.

To evaluate the influence of age on mortality, we have compared the survival at 15 and 30 years of our operated patients with the survival curves of the general Italian population (fig 3). The patients were divided into four groups according to their age at operation: group 1, 4–14 years; group 2, 15–24 years; group 3, 25–34 years; group 4, 35–48 years. Up to 15 years after the operation survival was not significantly different in the four groups of operated patients and in the general population. At 30 years, survival was significantly worse in groups 2 ($p < 0.003$) and 3 ($p < 0.00047$) than the general population. None of the 17 patients in the oldest age group (group 4) had died within 30 years of operation. This group is not included in fig 3, however, because the number of patients was too small for valid statistical analysis.

Patients who had an operation for coarctation lived longer than those who did not, but they did not have the life expectancy of the general population (fig 4). The percentage of survivors at the end of each decade up to the age of 30 equals that of the general population. But survival later decreases; however, the pattern of the curve remains similar to that of the general population.

Most survivors of surgical repair live normal lives: 81% are in New York Heart Association functional class I, 15% in class II, and 4% in class III.

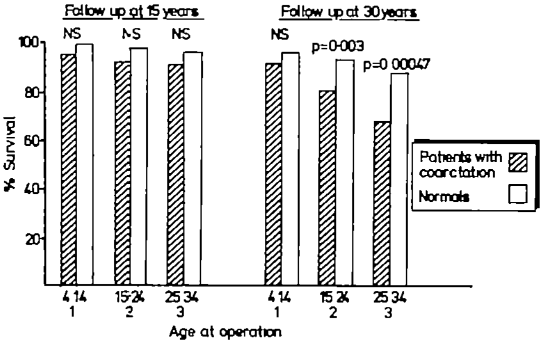

Fig 3 *Survival of patients at 15 and 30 years follow up divided into three groups (group 1, 65 patients; group 2, 67 patients; group 3, 60 patients) according to age at operation. The survival was compared with that of the general Italian population (ISTAT data for 1967–69)[18] of the same age group and for the same period of follow up.*

ELECTROCARDIOGRAM

The electrocardiogram was normal in 48% of the patients (68/143). Twenty one had signs of left ventricular hypertrophy; 10 of them had systemic hypertension, two had recoarctation, four had aortic valve disease, and five were normotensive without any associated anomaly. Fifteen patients had complete left bundle branch block and 15 had complete right bundle branch block. Two patients had a pacemaker because of complete heart block; both of them

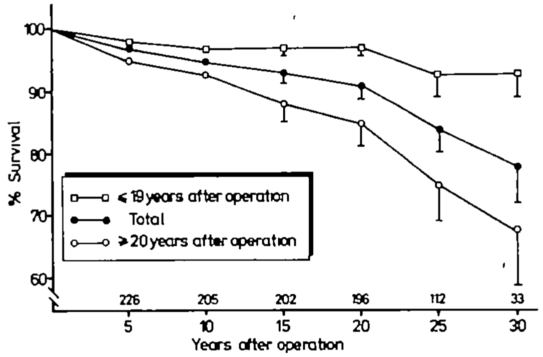

Fig 2 *Actuarial curves of patients excluding deaths in hospital. The middle curve shows the actuarial survival of all the patients. The upper and lower curves relate the chance of long term survival to age at operation. Absolute numbers are given on the horizontal axis.*

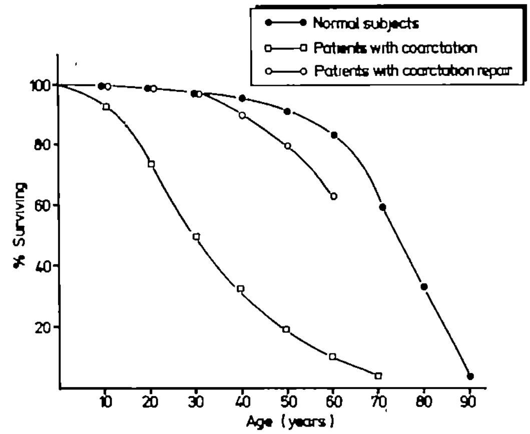

Fig 4 *Percentage of the subjects still alive at the end of each decade. The curve on the right (normal subjects) and the curve on the left (subjects with coarctation) are taken from Campbell[14] and the curve in the middle is drawn from our data.*

had severe aortic valve stenosis. Two patients had atrial fibrillation; one had ventricular septal defect and the other had mild aortic stenosis. One patient had a Wolff-Parkinson-White pattern; in 19 cases only non-specific ST-T changes were recorded.

ASSOCIATED ANOMALIES

The presence of associated abnormalities was diagnosed mostly on clinical and echocardiographic grounds. In a few patients the diagnosis was confirmed by cardiac catheterisation. Thirty eight (44%) of the 86 patients in whom either a cross sectional echocardiogram or an angiogram was obtained had evidence of a bicuspid aortic valve. Fourteen (9·8%) of 143 had moderate to severe aortic valve stenosis or insufficiency or both. Three patients had an aortic valve replacement 16–20 years after coarctation repair and four patients are awaiting operation. The seven remaining patients are being followed up.

There was clinical and echocardiographic evidence of mitral regurgitation in four; in two of them it was due to a mitral valve prolapse. A small ventricular septal defect was detected in two patients and another patient (aged 56) has a ventricular septal defect with a 2 8:1 shunt and is awaiting operation. In all cases the defects were perimembranous.

Two of three patients with discrete subaortic stenosis were operated on seven and nine years after coarctectomy. One had an additional supravalvar aortic stenosis relieved at operation. In the second patient a bicuspid aortic valve and an aneurysm of the perimembranous septum were also found at operation. In the third patient, who was not operated on, the stenosis was discovered by cross sectional echocardiogram 17 years after the operation.

In three patients dilated cardiomyopathy was discovered by cross sectional echocardiography 27–30 years after the surgical repair of the coarctation. In all angiography showed diffuse ventricular hypokinesia without coronary lesions. One of these patients had a 30 mm Hg pressure gradient across the aortic valve and severe mitral regurgitation due to dilatation of the annulus. Another had a 20 mm Hg pressure gradient across the coarctation but no aortic valve stenosis or regurgitation, and the third one had no residual gradient.

Three patients had clinical evidence of coronary artery disease.

RECOARCTATION

Fifteen of the 143 reassessed survivors had recoarctation; the gradient varied from 20 to 100 mm Hg. One patient had successful reoperation; six of the 26 patients who died during follow up had recurrent coarctation.

Eight per cent of the patients with end to end anastomosis and 35% of those in whom the intervention was of another type had a recurrent coarctation. This difference is statistically significant ($p < 0{\cdot}01$), whereas there is no difference between patients operated on at a younger or older age.

HYPERTENSION

Forty six of 128 patients had systemic hypertension without recoarctation. Figure 5 shows the actuarial curve for the presence of hypertension. Blood pressure was normal in most patients seen 10 years after operation, but later hypertension gradually became more frequent. Thirty years after coarctation repair only 32% of the patients are expected to be normotensive. Late hypertension was less common in patients operated on at younger ages (<20 years), but this difference was statistically significant only in the period between 15 and 25 years of follow up. The number of patients with a longer follow up was, however, small.

Because the incidence of hypertension in our population seemed to increase with the length of the follow up and therefore with the age of the patients, as it does in the general population, we compared the prevalence of hypertension in our population with that of the general Italian population for each decade.[9] In the patients who had surgical repair hypertension was more than 1·34 times more common than would be expected in the general Italian population ($\chi^2 = 4{\cdot}5$, $p < 0\ 05$). We also found that the standardised ratio for hypertension was 1 15 in the patients operated on before the age of 35 years (χ^2 not significant) and 1·37 in the patients operated on after that age ($\chi^2 = 4{\cdot}60$, $p < 0\ 05$). This means that the patients operated on at an older age are more

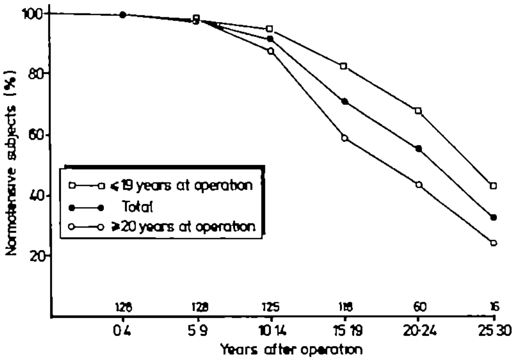

Fig 5 *Actuarial curves for continuing normotension in patients (absolute numbers are given on horizontal axis). The middle curve shows the actuarial percentage of normotensive patients among all the patients. The upper and lower curves relate the chance of long term normotension to the age at operation*

likely to become hypertensive than the general Italian population. Hence the difference between the two curves in fig 5 is due not only to the fact that one group of patients is older, but also to the fact that surgical repair was performed.

Patients with higher preoperative blood pressure had a tendency to have late hypertension. To assess this effect we examined preoperative and present blood pressure levels in the 97 patients in whom both were available after excluding patients with recoarctation. Hypertension was less common (25%) at the last postoperative examination in patients with a preoperative blood pressure of ⩽200 mm Hg than it was in those in whom the preoperative blood pressure was >200 mm Hg before operation (60%) ($p < 0.01$).

Multifactorial analysis (log linear model) shows that in patients with late postoperative hypertension there is a positive correlation with high preoperative blood pressure and with an older age at operation. This means that a patient who is >20 at operation with a very high blood pressure will have little chance of becoming and remaining normotensive after the operation.

Discussion

DOES COARCTATION REPAIR IMPROVE LIFE EXPECTANCY?

The goals of operation in aortic coarctation are prolongation of life and relief of symptoms, including normalisation of blood pressure. Our data confirm that life expectancy was significantly higher in our patients than in those who were not operated upon; however, it remains lower than in the general Italian population (fig 4). The shorter life expectancy after an apparently successful repair in our series was mostly the result of cardiovascular causes. Premature coronary artery disease, congestive heart failure, and cerebrovascular accidents, which were probably related to congenital aneurysms of brain arteries, were the commonest causes of death. Except for ischaemic heart disease, the causes of death in our patients resembled those reported by Campbell in a series of patients with coarctation that was not treated by surgical repair.[14]

IS AGE AT THE TIME OF OPERATION IMPORTANT?

Age at operation does not seem to influence survival during the first 15 years of follow up (fig 2). Afterwards life expectancy is significantly lower than in the general population in those in whom the operation was performed after the age of 14. Furthermore, all but one of our patients who died because of coronary artery disease were older than 20 at the time of coarctation repair.

No patients operated upon after the age of 35 died. Patients who survived to be operated on after 35 may have had the mildest form of the disease. The small number of such patients precludes any firm conclusion, however.

The three main problems encountered in patients operated on for coarctation were associated anomalies, recoarctation, and late hypertension.

ASSOCIATED ANOMALIES

A bicuspid aortic valve is common in patients with aortic coarctation. Careful follow up is necessary in these cases because clinically important aortic stenosis and insufficiency may develop. An important aortic valve lesion, which may have been related to the presence of bicuspid aortic valve, was found in about 10% of the patients. Some required operation.

Serious coronary heart disease seems to be common in our patients despite their youth. It was the commonest cause of late death. We cannot say whether coronary artery disease in such patients develops because of residual hypertension or because of associated anomalies.

Ventricular septal defect, mitral insufficiency, and dilated cardiomyopathies are rare. In the individual cases, however, these conditions can influence late outcome.

RECOARCTATION

As reported elsewhere[11 19] recoarctation was not a major problem in patients who were >4 years old if they had an end to end anastomosis (8%). Recurrences were rather common (35%), however, in those in whom different operative techniques (Clagett, prosthetic tube) were used. Such techniques are now seldom used.

LATE HYPERTENSION

About 30% of our patients had hypertension after coarctation repair. This figure is similar to that reported by others.[2 3 11 20] Hypertension is often associated with the development of recoarctation and its cause remains unknown. It is more frequent in patients operated upon after the age of 20 and it may appear 10–15 years after an apparently successful repair.

This is not solely due to the normal aging process, since the percentage of cases with arterial hypertension in patients with a successfully operated coarctation is higher than in the general population of the same age.

From our data it also appears that a high preoperative blood pressure predisposes the patient to the development of hypertension.

LIMITATION OF THE STUDY

Our patients were operated on between 1954 and 1969 and preoperative investigations were, therefore, limited; no intracardiac pressure measurements, no coronary angiography, no echocardiography, and only few aortograms were performed. The diagnosis of coarctation was always confirmed at surgery, however.

Not all patients had an annual examination; however, at least one intermediate blood pressure measurement was available and the time that hypertension reappeared could be determined with confidence. Furthermore, our own evaluation was mainly conducted on clinical grounds; invasive investigations were confined to patients in whom we suspected complications or additional anomalies or both. Not all patients had an echocardiographic examination. Our study group included 25 patients who had operations (mainly Clagett's procedure) that have subsequently been abandoned.

Conclusions

A successful coarctectomy prolongs life. The benefits of the operation are, however, limited by age and severe hypertension at operation, and by associated anomalies and premature coronary artery disease. Recoarctation is uncommon but the incidence of unexplained recurrent hypertension is high.

We thank Professor A Dato who operated on most of the patients we reviewed.

References

1 Crafoord C, Nylan G. Congenital coarctation of the aorta and its surgical treatment. *J Thorac Surg* 1945;14.347–61.

2 Liberthson R, Pennington D, Jacobs M, *et al.* Coarctation of the aorta: review of 234 patients and clarification of management problems. *Am J Cardiol* 1979;43:835–40.

3 Maron BJ, Humphries O, Rove RD, *et al.* Prognosis of surgically corrected coarctation of the aorta. A 20 years postoperative appraisal. *Circulation* 1973;47:119–26.

4 Menasche Ph, Blondeau Ph, D'Allaines C, *et al.* Résultats lointains de la correction chirurgicale de la coarctation de l'aorte. Étude de 90 malades opérés depuis il à 15 ans. *Arch Mal Coeur* 1978;1:181–90.

5 Simon AB, Zloto AE, *et al.* Coarctation of the aorta. Longitudinal assessment of operated patients. *Circulation* 1974;50:456–64.

6 Morino F, Santarelli P, Lino R, *et al.* Coartazione dell'aorta. Risultati a distanza del trattamento chirurgico a proposito di 113 casi seguiti fino a 10–12 anni dall'intervento. *Minerva Cardioangiol* 1976;24:799–815.

7 Pollack P, Freed MD, Castaneda AR, *et al.* Reoperation for isthmic coarctation of the aorta: follow-up of 26 patients. *Am J Cardiol* 1983;51:1690–4.

8 Clagett OT. Coarctation of the aorta; surgical aspect. *Proc Staff Meet Mayo Clin* 1948;23:359–63.

9 Ambrosio GB, Bulgaro L, Gabaldo S, *et al.* Blood pressure and its spontaneous variations in the northern Italian population. *Clin Sci Mol Med* 1976;51:669–710.

10 Kaplan N. Systemic hypertension mechanism and diagnosis. In: Braunwald E, ed. *Heart disease. A text book of cardiovascular medicine.* Philadelphia: WB Saunders, 1980:852–921.

11 Clarkson PM, Nicholson MR, Barrat-Boyes BG, *et al.* Results after repair of coarctation of the aorta beyond infancy: a 10 to 28 years follow-up with particular reference to late systemic hypertension. *Am J Cardiol* 1983;51:1481–8.

12 Connor PM, Baker WP. A comparison of coarctation resection and patch angioplasty using post exercise blood pressure measurement. *Circulation* 1981;64:567–72.

13 Colton T. *Statistics in medicine.* Boston: Little Brown, 1975.

14 Campbell M. Natural history of coarctation of the aorta. *Br Heart J* 1970;32:633–40.

15 Ambrosio GB, Zambon S, Varnizzo D, *et al.* La prevalenza di ipertensione arteriosa nella comunità. L'esperienza del Veneto. *G Ital Cardiol* 1980, 10:1280–7.

16 Rose G, Barker DJP. Comparing rates. *Br Med J* 1978;ii:1282–3.

17 Brown M. *Multiway frequency tables. The log-linear model.* Los Angeles: University of California Press, 1981.

18 ISTAT. *La popolazione italiana.* Rome: Poligrafico dello Stato, 1982.

19 Naton MA, Olley PM. Residual hypertension after coarctectomy in children. *Am J Cardiol* 1976;37:769–72.

20 Björk VO, Begdahl L, Jonasson R, *et al.* Coarctation of the aorta. The world's longest follow-up. *Adv Cardiol* 1978;22:205–15.

Br Heart J 1987;57:468–73

Alcohol and new onset atrial fibrillation: a case-control study of a current series

PEKKA KOSKINEN, MARKKU KUPARI, HANNU LEINONEN,
KIMMO LUOMANMÄKI

From the First Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland

SUMMARY The aetiological role of alcohol in new onset atrial fibrillation was evaluated in a case-control study of 100 consecutive patients aged 21–64 years. Clinical examination, routine diagnostic tests, and echocardiography revealed an underlying disease or other identifiable factor for atrial fibrillation in 65 patients (group 1); 35 patients had idiopathic atrial fibrillation (group 2). The most common diseases associated with atrial fibrillation were ischaemic heart disease (21%), hypertension (13%), and cardiomyopathy (8%). Data on alcohol consumption were obtained by interviewing the patients and their age and sex matched controls on admission. The mean daily alcohol intake of group 2 patients during the week preceding atrial fibrillation was significantly larger than that of either their controls or group 1 patients. Compared with controls significantly more patients in both groups with atrial fibrillation had consumed alcohol within two days of the onset of the arrhythmia. Significantly more patients had onset of arrhythmia on Wednesday, Thursday, or Friday than on any other weekday, including patients with high alcohol intake.

This study establishes alcohol as an important precipitating factor for new onset atrial fibrillation.

Alcohol has recently been incriminated as a common precipitating factor for atrial fibrillation,[1–3] and electrophysiological studies have verified its arrhythmogenicity in long term alcoholics.[4 5] Not only habitual heavy drinkers seem to be liable to arrhythmias; even apparently healthy moderate or infrequent drinkers may suffer an episode of atrial fibrillation after an alcohol binge.[6–8]

The incidence of alcohol related arrhythmias is uncertain and may vary between populations with different alcohol cultures. All previous studies on the subject have been either retrospective surveys or isolated case reports. In one study, up to 47% of all new cases of atrial fibrillation in middle aged patients were thought to be caused by alcohol,[1] whereas other reports have given rates from less than 30%[8] to 63%[2] of otherwise unexplainable atrial fibrillation.

We have recently began a series of studies to evaluate the frequency and clinical importance of alcohol related arrhythmias in the emergency ward of our hospital. In the present report we describe the aetiological factors in 100 consecutive young and middle aged patients with new onset atrial fibrillation and compare their drinking habits with those of a matched control patient population.

Patients and methods

The study was carried out between 1 January and 20 September 1985 in the emergency ward of Helsinki University Central Hospital. The hospital serves a population of approximately 900 000 and there are 1600–1900 patient visits every month to the emergency ward. During the study period 101 patients aged <65 years were admitted for their first documented episode of atrial fibrillation. These were the patients that we studied.

AETIOLOGICAL EVALUATION

The patients were examined by a cardiologist on the day of admission or the next morning, when sinus rhythm had been restored in almost all of them. The

Requests for reprints to Dr Markku Kupari, Cardiovascular Laboratory, Helsinki University Central Hospital, SF-00290 Helsinki, Finland.

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identification of cardiac or non-cardiac diseases was based on history and clinical examination complemented by chest *x* rays, cross sectional and M mode echocardiographic examination (Irex System III echocardiograph), blood tests (Coulter autoanalyser), serum sodium and potassium (ion selective electrode), calcium (enzymatic or atomic absorption spectrophotometry), magnesium (atomic absorption spectrophotometry), aspartate and alanine aminotransferases (enzymatic), γ glutamyl transpeptidase (enzymatic), creatine kinase isoenzymes (enzymatic and electrophoretic), thyroxine (radioimmunoassay), triiodothyronine uptake (radioimmunoassay and Sephadex uptake), and blood ethanol (enzymatic). Lung function was studied if this was needed to confirm or exclude the presence of pulmonary disease.

ASSESSMENT OF DRINKING HABITS

At admission every patient was questioned by one of us about the types and amounts of alcoholic beverages they had consumed each day during the week preceding the arrhythmia. The total amount of alcohol was recorded as grams of ethanol. The patients were also asked to estimate if this was more or less, or approximately the same they were accustomed to. If the patient was not aware of the time of onset of atrial fibrillation information about alcohol intake during the week before admission was collected. The patients were also asked the number of weeks they had been totally abstinent during the past year. Blood ethanol concentration on admission was not measured in all patients because the first laboratory tests were ordered by the attending physician and not one of the investigators. The smoking and coffee drinking habits of the patients and controls were also recorded.

CONTROL PATIENTS

After the case had been identified the diagnoses on emergency ward records were checked to find a suitable control patient. The control patient had to be of the same age (±10 years) and sex as the case and the diagnosis or symptom for hospital admission had to be one of an acute illness. The majority of the controls were found and interviewed on the same day as the cases, and the rest were found within two or three days. They too were questioned about their alcohol and coffee consumption and smoking habits in the week before admission. We did not select the controls totally randomly because hospital patients are not a representative sample of the population. By excluding patients admitted with conditions known to be alcohol related, such as acute pancreatitis or drug intoxications, and with severe chronic diseases, such as cancer, we tried to avoid overrepresentation of heavy drinkers and abstainers, respectively, in our control population. We also excluded patients admitted for acute cardiac diseases because the present study is part of a large project designed to evaluate the role of alcohol in various cardiac emergencies. Table 1 lists the diagnoses and symptoms of the control patients.

Table 1 *The referral diagnoses or symptoms of the control patients*

Diagnosis or symptom	*No*
Acute asthma or bronchitis	11
Suspicion of deep venous thrombosis	11*
Ureteral colic	10
Pneumothorax (2 traumatic, 7 spontaneous)	9
Miscellaneous acute infectious disease	8
Acute appendicitis	7
Pleuropneumonia	7
Erysipelas	3
Minor traumas	3
Headache	3
Hernias	3
Miscellaneous (wound infection, haematuria, abdominal pain, vertigo)	23

*Deep venous thrombosis was confirmed by venography in eight patients

STATISTICAL ANALYSIS

The statistical comparisons between cases and controls were performed by McNemar's test when there were only two outcomes and Stuart-Maxwell statistics[9] when there were more. We also tested for a linear trend in the (log) risk of atrial fibrillation with increasing alcohol consumption.[10] The atrial fibrillation groups were compared by the χ^2 test and Student's *t* test for independent data. The distribution of the onset of the arrhythmia between different weekdays was analysed by a χ^2 test for goodness of fit.

Results

There were 19 women and 82 men (mean age 48 years (range 21–64)). The mean age of the controls was also 48 years. One patient, a male alcoholic, could not be examined and he was excluded from the analysis. Data on alcohol and coffee drinking and smoking were obtained in 98 patients; one patient died of diabetic coma and pneumonia before he could be interviewed and one patient admitted after an electrical shock did not answer the questions. Cross sectional echocardiograms were obtained in 95 patients; two patients refused echocardiography (an otherwise healthy 21 year old man and a male alcoholic with previous myocardial infarction) and one patient died of acute myocardial infarction before the

Table 2 *Diseases associated with new onset atrial fibrillation*

	No
Coronary heart disease:	
Acute myocardial infarction	7
Old myocardial infarction	7
Angina pectoris	7*
Total	*21***
Hypertension	13
Cardiomyopathy:	
Dilated	4
Hypertrophic	4
Total	*8*
Chronic obstructive pulmonary disease	5
Previous myopericarditis	4
Mitral valve disease	
Rheumatic	2
Prolapse	1
Total	*3*
Ischaemic heart disease with normal coronary arteries	2
Athletic heart syndrome	2
Electrical shock	2
Aortic valve disease	1
Pre-excitation syndrome	1
Toxic shock with myopericarditis	1
Thyrotoxicosis	1
Diabetic ketoacidosis with pneumonia	1
Idiopathic	35

*1 patient also had pulmonary embolism, **5 patients also had hypertension

examination. Good quality echocardiographic recordings were obtained in 85 patients.

DISEASES AETIOLOGICALLY ASSOCIATED WITH ATRIAL FIBRILLATION

Sixty five patients (group 1) had a disease or other identifiable factor that could be aetiologically associated with atrial fibrillation (table 2). Twenty one of them had coronary heart disease; seven gave a history of typical effort related angina pectoris and 14 had acute or old myocardial infarction indicated by a history of prolonged chest pain and changes in the electrocardiogram or in serum enzymes or in left ventricular echocardiography. Hypertension was diagnosed in 18 patients; 16 were on antihypertensive treatment and two patients with previously undiagnosed hypertension had supine diastolic blood pressure >110 mm Hg in repeated measurements after admission. Five of the hypertensive patients also had coronary heart disease. Only four patients had hypertensive left ventricular disease (wall thickness > 14 mm on echocardiography). Dilated cardiomyopathy was diagnosed in four patients who had heart failure without other explanation and diffusely poor contraction of the left ventricle with an increased diastolic dimension (>60 mm) on echocardiography. Another four patients had the hypertrophic form of cardiomyopathy; the electrocardiogram showed increased left ventricular voltages in all, and the septal or free wall thickness exceeded 14 mm on echocardiography. Five patients had chronic obstructive pulmonary disease; they gave a long history of productive cough and dyspnoea without heart disease and clinical examination, chest *x* rays, or lung function tests supported this diagnosis. Old myopericarditis was diagnosed in four patients and acute myopericarditis in one; all gave a history of a febrile illness (diphtheria in one, rheumatic fever in one, acute toxic shock in one, unspecified in two) and had localised or diffuse abnormalities of myocardial contractions and pericardial thickening or effusion on echocardiography. Significant valvar disease was found in four patients (one rheumatic mitral stenosis, one rheumatic mitral regurgitation, one aortic regurgitation, and one mitral valve prolapse). One of the patients had undergone cardiac catheterisation; in others the diagnosis was based on clinical and echocardiographic examinations. Athletic heart syndrome[11] was diagnosed in two patients; both had a long history of endurance training and an increased left ventricular end diastolic diameter (>56 mm) on echocardiography without impairment of left ventricular systolic function. Two patients had syndrome X (ischaemic heart disease despite patent coronary arteries); both had previously undergone coronary angiographic and perfusion studies.[12] Other illnesses diagnosed in group 1 were thyrotoxicosis (one patient), pre-excitation syndrome (one patient), and diabetic coma with pneumonia (one patient). Two patients had onset of arrhythmia after an electrical shock.

In 35 patients (six women and 29 men) we found no evidence of concomitant cardiac or non-cardiac disease (group 2).

DATA ON ALCOHOL CONSUMPTION

Nine patients (three women, six men) in group 1 and 10 (five women, five men) controls had not drunk any alcohol during the past year. In group 2, five patients (three women, two men) and five controls (one woman, four men) had been teetotallers for the whole year. Table 3 shows the patients' and controls' estimates of their alcohol consumption for the week

Table 3 *Estimation of alcohol consumption during the week before atrial fibrillation compared with normal use in cases and controls*

	Alcohol consumption			
	More	*Less*	*The same*	*p*
All cases/controls	17/9	4/12	77/77	<0 05
Group 1/controls	8/4	2/9	53/50	NS
Group 2/controls	9/5	2/3	24/27	NS

Group 1, atrial fibrillation with an aetiologically associated disease.
Group 2, idiopathic atrial fibrillation

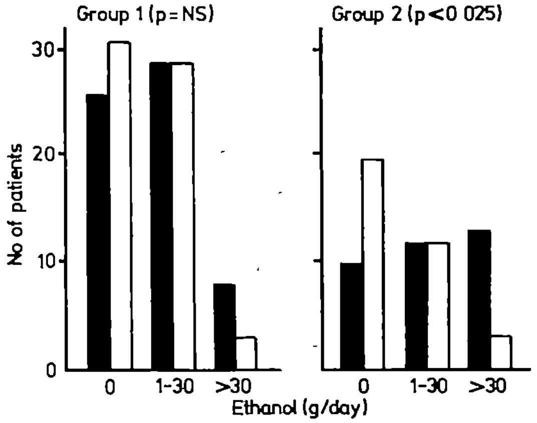

Fig 1 *Average daily alcohol consumption of the patients (black columns) and their controls (white columns) during the week preceding the atrial fibrillation. Group 1, atrial fibrillation with an associated disease. Group 2, idiopathic atrial fibrillation.*

preceding atrial fibrillation compared with their normal alcohol intake.

To analyse the data on the average amount of alcohol consumed daily during the week before atrial fibrillation we divided the patients and controls into three groups: (*a*) abstainers; (*b*) those with an average daily consumption of 1–30 g of ethanol; (*c*) those with an average daily alcohol consumption of > 30 g of ethanol. Figure 1 shows the distribution of the patients and controls in these groups. Patients with atrial fibrillation had drunk more than the controls ($\chi^2 = 10{\cdot}407$; $p < 0{\cdot}01$). This difference came mainly from group 2 patients whose alcohol consumption had been significantly larger than that of their controls ($\chi^2 = 8{\cdot}658$; $p < 0{\cdot}025$) whereas the difference between patients in group 1 and their controls was not statistically significant ($\chi^2 = 2{\cdot}531$; p = NS). The (log) risk of atrial fibrillation increased linearly with alcohol use in all cases ($\chi^2 = 8{\cdot}880$; $p < 0{\cdot}025$) and also in group 2 ($\chi^2 = 8{\cdot}266$; $p < 0{\cdot}025$).

Table 4 *Frequency of abnormal laboratory findings in patients with new onset atrial fibrillation*

Variable		*Group 1*	*Group 2*
MCV	>96 fl	6 (57)	1 (29)
Serum potassium	<3·7 mmol/l	12 (59)	8 (35)
	<3·0 mmol/l	1 (59)	2 (35)
Serum calcium	<2·25 mmol/l	27 (54)	10 (30)
	<2·10 mmol/l	3 (54)	2 (30)
Serum magnesium	<0·70 mmol/l	5 (51)	3 (27)
S-ASAT	>40 IU/l	5 (53)	8 (33)
S-ALAT	>40 IU/l	10 (54)	10 (32)
S-γ-GT	>50 IU/l	18 (53)	8 (31)
Blood ethanol	>1 mmol/l	5 (12)	7 (17)

The figures in parentheses are the number of patients tested.
MCV, mean red cell corpuscular volume; S-ASAT, aspartate aminotransferase (serum), S-ALAT, alanine aminotransferase (serum); S-γ-GT, γ glutamyl transpeptidase (serum).
Group 1, atrial fibrillation with an aetiologically associated disease.
Group 2, idiopathic atrial fibrillation.

Seven of the patients with atrial fibrillation had used alcohol heavily (> 75 g of ethanol daily) during the week preceding the arrhythmia: five of 35 in group 2 (*vs* none of their controls) and two of 63 in group 1 (*vs* one of their controls).

Alcohol use immediately before the arrhythmia was evaluated separately by our noting whether or not the cases and controls had drunk any alcohol during the two days preceding the arrhythmia or admission. There were 25 drinkers in group 1 (*vs* 13 controls; $\chi^2 = 4{\cdot}321$, $p < 0{\cdot}05$) and 19 of 35 in group 2 (*vs* 4 controls; $\chi^2 = 11{\cdot}529$; $p < 0{\cdot}001$). Twelve of the 29 patients whose blood ethanol concentration was measured on admission had been drinking recently. Their blood ethanol concentration was over 1 mmol/l (table 4).

DATA ON COFFEE DRINKING AND SMOKING

Coffee drinking and smoking habits were not significantly different in cases and controls. In group 1, 78% of cases and 83% of controls drank coffee daily and 35% of both cases and controls were current smokers. In group 2, 77% of cases were coffee drinkers and 34% were smokers; the corresponding figures for the controls were 89% and 29%.

COMPARISONS BETWEEN THE TWO GROUPS WITH ATRIAL FIBRILLATION

Group 1 patients were significantly ($p < 0{\cdot}001$) older than those of group 2 (mean age 52 and 43 years, respectively), but there was no difference in the sex distribution. Patients in group 2 had used significantly larger amounts of alcohol daily during the week preceding atrial fibrillation than those in group 1 ($\chi^2 = 7{\cdot}753$; $p < 0{\cdot}025$) (fig 1). In contrast there was no statistical difference between the groups for alcohol use in the two days before atrial fibrillation; 38% in group 1 and 54% in group 2 had used alcohol during that time.

Table 4 shows the frequencies of abnormal laboratory findings. There were no statistically significant differences between the groups for any of the laboratory measurements. Fifty per cent of cases in group 1 and 54% in group 2 who had drunk >30 g of ethanol daily had one or more of the liver enzyme values above normal limits. Only one patient in the highest alcohol consumption category had increased mean red cell corpuscular volume. The abnormally low electrolyte values were evenly distributed between the groups and they were not related to the amount of alcohol used.

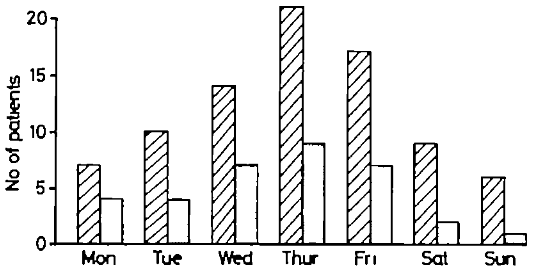

Fig 2 *Distribution of the onset of atrial fibrillation in 84 patients by days of the week. The hatched columns indicate patients with atrial fibrillation and an associated disease and the stippled columns show patients with idiopathic atrial fibrillation.*

VARIATION BY WEEKDAYS IN THE ONSET OF ATRIAL FIBRILLATION

Eighty four patients (50 in group 1 and 34 in group 2) were certain of the day on which arrhythmia had started. Figure 2 shows the day by day distribution of the onset of atrial fibrillation in both groups. The distribution differed significantly from a chance occurrence ($\chi^2 = 15\ 332$; $p < 0{\cdot}025$) with the highest frequencies occurring in the middle of the week. In both groups 1 and 2 there was a similar trend but this did not quite reach statistical significance. Patients with high alcohol consumption showed a similar variation by weekday as did other cases. Fourteen (70%) of those 20 patients who had consumed >30 g/day during the previous week had onset of arrhythmia on Wednesday, Thursday, or Friday.

Discussion

Taken together with earlier investigations,[1-3] our study strongly supports the idea that alcohol plays a significant role in the genesis of otherwise inexplicable atrial fibrillation. The frequency of alcohol related atrial fibrillation, however, was clearly lower in our study than in two recent retrospective studies.[1 2] Only one third of patients admitted for idiopathic atrial fibrillation had consumed more than 30 g of ethanol daily during the preceding week and not more than five of 35 patients had had more than 75 g a day. These data suggest that in about 15–30% of patients with idiopathic atrial fibrillation the arrhythmia may be alcohol related and that about 5–10% of all new episodes of atrial fibrillation can be explained by alcohol use. Among other identifiable diagnoses associated with new onset atrial fibrillation (table 2) alcohol abuse would thus rank above well-known factors such as valvar heart disease, chronic obstructive pulmonary disease, and thyrotoxicosis. The true aetiological contribution of alcohol to atrial fibrillation may be somewhat larger because by causing dilated cardiomyopathy[13] or myocardial infarction despite patent coronary arteries[14] it can be the primary, although not the immediate, cause of the arrhythmia. Two of our four patients with dilated cardiomyopathy were alcoholics; they denied recent drinking. As well as being the main cause of atrial fibrillation in some patients, alcohol may be a triggering factor in patients with other heart diseases. This is suggested by our finding that a larger proportion of patients with aetiologically identifiable atrial fibrillation than of controls had used alcohol within the two days preceding the onset of the arrhythmia.

The selection of control patients in a hospital based study is always difficult and open to criticism. In our study, however, the alcohol consumption of the controls resembled that of a representative sample of 15–69 year old Finns whose alcohol use was studied in 1984.[15] In that study 3870 people were questioned in detail about their drinking habits during one week and their alcohol use in general during the past year was evaluated. Twenty seven per cent of women and 12% of men had abstained in the previous year. The calculated mean yearly alcohol consumption (alcohol used during the week in question times 52) of the male drinkers was 4·1 kg (median 1 9 kg) of ethanol and for female drinkers it was 1·1 kg (median 0·4 kg). In our control group the frequencies of teetotallers (32% in women, 11% in men) were very close to those found in the population study. Mean yearly ethanol consumption of those controls who had drunk alcohol during the past year was 3·8 kg (median 1·5 kg) in men and 0·2 kg (median 0) in women. The consumption of our male controls accords well with the population study whereas that of our female patients seems too small. There were only 13 drinkers among our female controls, however, and this may partly explain the discrepancy, especially as we evaluated only one week's alcohol intake. An important finding was that the patients with atrial fibrillation had drunk much larger quantities of ethanol: the mean values for yearly consumption were 9·1 kg (median 5·3 kg) in male drinkers and 6 3 kg (median 0) in female drinkers. In our view these data support our conclusion that atrial fibrillation may be precipitated by a high intake of alcohol.

Probable mechanisms by which alcohol may induce atrial fibrillation have been discussed recently.[15] Alcohol can increase the concentration of circulating catecholamines,[16] change conduction times and refractory periods in the myocardium,[4 5 17] evoke sudden increases in vagal tone (vomiting), and produce subclinical myocardial injury when used heavily for many years.[13] It may well be that in most cases a combination of two or more of these influences triggers the arrhythmia after binge drinking. It is our impression that factors such as physical or mental stress, lack of sleep, or febrile respiratory infections may at times increase the arrhythmogenic capacity of alcohol, probably by augmenting the basal sympathoadrenergic tone. In the present study electrolyte disturbances were not related to alcohol use and most patients had serum electrolytes within normal range on admission, although there were a surprising number with marginally lowered concentrations of serum total calcium. Unfortunately, serum albumin and ionised calcium were not measured, so there is no proof of real hypocalcaemia in these patients.

The term "holiday heart", introduced by Ettinger *et al*,[3] has been widely adopted to describe alcohol related arrhythmias clustering after the weekend and after holidays such as Christmas and New Year. In our study, however, the frequencies of the onset of atrial fibrillation were lowest during the weekend and in the days afterwards and highest in the middle of the week, irrespective of the aetiology of the arrhythmia. Nor did we see any excess of cases after festivals such as the New Year, May Day, or Midsummer Day which are all associated with alcohol sprees in Finland. In their retrospective study, Rich *et al* did not find clusters of admissions for alcohol related atrial fibrillation after weekends or holidays.[2] It is possible that occupational mental or physical stress, which increases during the working week, together with other factors such as alcohol contribute to the onset of fibrillation.

Our study shows that ischaemic heart disease, hypertension, and cardiomyopathy are currently the most common diseases associated with new onset atrial fibrillation in young and middle aged population. Mitral valve disease and thyrotoxicosis, both still cited in textbooks as important causes of atrial fibrillation, now seem to be rare in this age group. About one third of patients presenting with their first episode of atrial fibrillation do not have any recognisable heart disease but many of them (15–30%) are frequent drinkers and some drink quite heavily. There is no doubt that alcohol should be included among the most common aetiological factors causing atrial fibrillation in those of working age.

References

1 Lowenstein AJ, Gabow PA, Cramer J, Oliva PB, Ratner K. The role of alcohol in new-onset atrial fibrillation. *Arch Intern Med* 1983;**143**:1882–5.

2 Rich EC, Siebold C, Campion B. Alcohol-related acute atrial fibrillation. A case-control study and review of 40 patients. *Arch Intern Med* 1985;**145**:830–3.

3 Ettinger PO, Wu CF, De La Cruz C, Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "holiday heart": alcohol-associated cardiac rhythm disorders. *Am Heart J* 1978;**95**:555–62.

4 Greenspon AJ, Shchaal SF. The "holiday heart"· electrophysiologic studies of alcohol effects in alcoholics. *Ann Intern Med* 1983,**98**:135–9.

5 Engel TR, Luck JC. Effect of whisky on atrial vulnerability and "holiday heart". *J Am Coll Cardiol* 1983;**1**:816–8.

6 Thornton JR. Atrial fibrillation in healthy non-alcoholic people after an alcoholic binge. *Lancet* 1984;**ii**:1013–4.

7 Lamb LE, Pollard LW. Atrial fibrillation in flying personel. Report of 60 cases. *Circulation* 1964,**29**:694–701.

8 Peter RH, Gracey JG, Beach TB. A clinical profile of idiopathic atrial fibrillation. A functional disorder of atrial rhythm. *Ann Intern Med* 1968;**68**:1288–95.

9 Fleiss JL, Everitt BS. Comparing the marginal totals of square contingency tables. *Br J Math Stat Psychol* 1971;**24**:117–23.

10 Breslow NE, Day NE. *Statistical methods in cancer research*. Lyon: International Agency for Research on Cancer, 1980:182–8.

11 Huston TP, Puffer JC, Rodney WM. The athletic heart syndrome. *N Engl J Med* 1985;**313**:24–32.

12 Virtanen KS. Evidence of myocardial ischaemia in patients with chest pain syndromes and normal coronary angiograms *Acta Med Scand [Suppl]* 1984;**694**:58–68.

13 Bridgen W, Robinson J Alcoholic heart disease. *Br Med J* 1964;**ii**.1283–9.

14 Regan TJ, Wu CF, Weisse AB, Moschos CB, Ahmed SS, Lyons MM. Acute myocardial infarction in toxic cardiomyopathy without coronary obstruction. *Circulation* 1975;**51**:453–61.

15 Simpura J, ed. *Finnish drinking habits Results from interview surveys in 1968, 1976 and 1984*. Helsinki Finnish Foundation for Alcohol Studies, 1987.

16 Anonymous. Alcohol and atrial fibrillation. *Lancet* 1985;**i**:1374.

17 Perman ES. The effect of ethyl alcohol on the secretion from adrenal medulla in man. *Acta Physiol Scand* 1958;**44**:241–7.

18 Gould L, Reddy CVR, Becker W, Oh K-C, Kim SG. Electrophysiologic properties of alcohol in man. *J Electrocardiol* 1978;**11**:219–26.

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Absent right superior caval vein (vena cava) with normal atrial arrangement

JUNG Y CHOI,* ROBERT H ANDERSON,† FERGUS J MACARTNEY*

*From the *Department of Paediatric Cardiology, The Hospital for Sick Children, Great Ormond Street, and the †Cardiothoracic Institute, London*

SUMMARY Eight cases of absent right superior caval vein (vena cava) with normal atrial arrangement from the Great Ormond Street database were reviewed. In each case the right subclavian vein and jugular vein drained into a persistent left superior caval vein through a bridging vein. In six cases the left superior caval vein drained into the right atrium by way of the coronary sinus, and in two cases it drained into the left atrium directly because of the complete unroofing of the coronary sinus. The frontal plane P wave axis was displaced leftwards and upwards in four out of seven cases in which an electrocardiogram was available. No case showed arrhythmia on a standard electrocardiogram preoperatively. Echocardiograms were available in four cases and in each case diagnosis of the anomalous connections of the systemic vein was possible. Only one third of the cases showed a crescentic shadow of the persistent left superior caval vein on chest *x* ray.

A chest *x* ray and electrocardiogram do not provide the means of reliable diagnosis of this condition, though they may suggest the possibility of its existence. Definitive diagnosis requires cross sectional echocardiography or angiocardiography or both.

Systemic venous anomalies are not uncommon in congenital heart disease particularly in atrial isomerism. When the atria are normally arranged a persistent left superior caval vein (vena cava) is the most common systemic venous anomaly and usually drains into the right atrium by way of the coronary sinus.

Absence of the right superior caval vein in atrial situs solitus is very rare and may present with either total absence of superior vena cava or partial absence above the azygos vein.[1 2] When the right superior caval vein is absent there is always a left superior caval vein that usually empties by way of the coronary sinus into the right atrium.[3 4] The left superior caval vein may join the left atrium directly in patients with normal atrial arrangement, in which case all the systemic venous blood from the upper half of the body drains into the left atrium.[5 6]

A persistent left superior caval vein draining into the right atrium by way of the coronary sinus is haemodynamically insignificant unless the patient is to undergo cardiopulmonary bypass, a surgical procedure involving the systemic veins, or pacemaker insertion.[7–10] When the left superior caval vein drains directly into the left atrium it can produce a right to left shunt and cyanosis.[11]

A persistent left superior caval vein is often associated with leftward deviation of the P wave axis and other arrhythmias.[3 9 12] There has been a debate on the mechanism of these arrhythmias and abnormal histological findings in the conduction system have been reported.[2 13]

The diagnosis of persistent left superior caval vein once required diagnosis by catheterisation or angiocardiography or both, but now non-invasive diagnosis by echocardiography is possible.[14]

Patients and methods

The Great Ormond Street database, consisting of computerised records of necropsies since 1940 and diagnoses in life since 1972, was searched for cases of absent right superior caval vein in patients with normal atrial arrangement and absent left superior caval vein in those with inverted atria. Eight patients in the former category were found and none in the latter. Patients with atrial isomerism were excluded. Cardiac catheterisation and angiocardiography were

Requests for reprints to Professor Fergus J Macartney, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH

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Table *Cardiac anomalies in eight cases of absent right superior caval vein*

Case No.	*Age*	*Sex*	*Cardiac anomalies*
1	2 yr 5 mnth	M	Solitus, discordant, single outlet heart with aorta from right ventricle. Pulmonary atresia. Dextrocardia. VSD, ASD, DA
2	2 yr 8 mnth	M	Normal connections. VSD
3	1 yr 8 mnth	F	Normal connections. TOF. Right aortic arch
4	5 yr 7 mnth	F	Normal connections. TOF
5	7 mnth	M	Normal connections. Left superior caval vein to left atrium because of complete unroofing of coronary sinus
6	1 day	M	Solitus, concordant, single outlet heart with aorta from right ventricle. VSD, DA. Left juxtaposition of atrial appendages. Right aorta arch. Complete unroofing of coronary sinus
7	2 wk	M	Solitus, concordant, single outlet truncus arteriosus. ASD, VSD
8	5 yr 6 mnth	M	Normal connections. Coarctation of aorta

VSD, ventricular septal defect; ASD, atrial septal defect; DA, ductus arteriosus; TOF, tetralogy of Fallot.

carried out in all cases and heart surgery was performed in six. Necropsy specimens were available in two cases.

Results

There were eight cases of absence of right superior caval vein. All had other cardiovascular anomalies (table). In each case the right jugular and subclavian veins drained into the left superior caval vein by way of a bridging brachiocephalic vein. The left superior caval vein drained into the right atrium by way of the coronary sinus in six cases. In two cases the left superior caval vein drained into the left atrium because of complete unroofing of the coronary sinus. The only remnant of the coronary sinus was its orifice, which mimicked an atrial septal defect. Pathological specimens were available in cases 6 and 7. In both cases there was no remnant of the right superior caval vein, not even a fibrous chord.

Standard electrocardiograms were available in seven cases. Frontal plane P wave axes were variable, ranging from -30° to 60°. Four cases showed an upwards and leftwards deviation of the P wave axis, but in no case was deviation extreme (less than -30°). In three cases the P wave axis was within the normal range (0–90°). P-R intervals were in the normal range except in one case which showed a shortened P-R interval (0·10 s), no P-R segment, and a normal P wave axis. No case showed any arrhythmia preoperatively on a standard electrocardiogram. Conduction anomalies developed in three cases after operation. In case 4 complete right bundle branch block developed after total correction of tetralogy of Fallot. Case 5 showed transient second or third degree heart block during the first three days after an operative procedure in the coronary sinus area. The cardiac rhythm returned to normal three days after operation and a follow up electrocardiogram did not show any arrhythmia. In case 3 complete right bundle branch block developed after total correction of tetralogy of Fallot and 24 hour electrocardiographic monitoring showed sinus slowing with junctional escape during sleep. The QRS axis and evidence of ventricular hypertrophy varied depending on the associated intracardiac anomalies. There were no cases with intraventricular conduction abnormalities before surgery.

Chest *x* rays were available in seven cases. Cardiac size and shape and pulmonary vascular markings depended upon the associated cardiac defects. The superior mediastinal shadow on both sides of the spine was evaluated. A crescentic vascular shadow passing from the upper left border of the aortic arch towards the middle third of the left clavicle was evident in two cases out of seven. Case 2 showed a decreased mediastinal shadow to the right of the

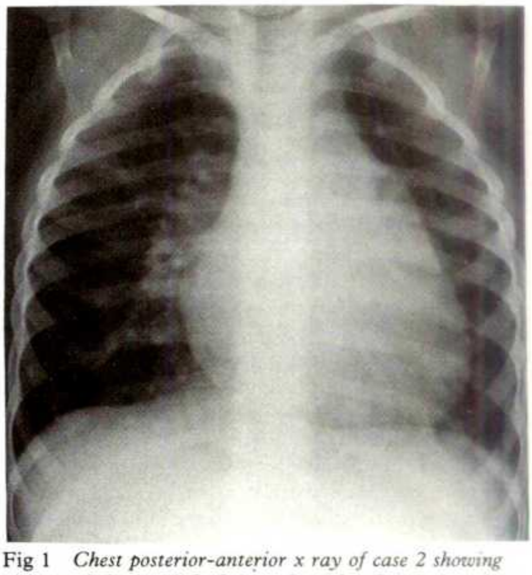

Fig 1 *Chest posterior-anterior x ray of case 2 showing absence of the usual shadow to the right of the spine above the right atrial shadow suggesting absence of right superior caval vein.*

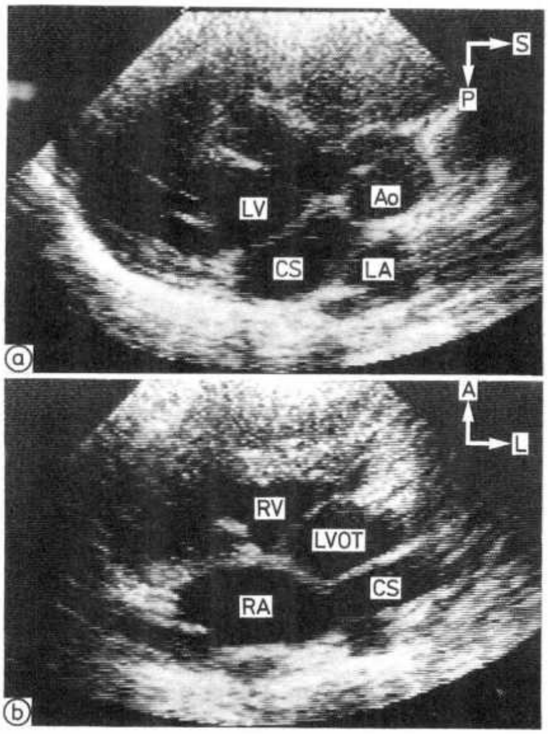

Fig 2 *Cross sectional echocardiogram of case 2. Upper picture is a precordial long axis cut showing dilated coronary sinus (CS) which looks like a tubular structure in the left atrium (LA). Lower picture is a precordial short axis cut just below the aortic valve showing the coronary sinus draining into the right atrium (RA). A, anterior; Ao, aorta; L, left; LV, left ventricle; LVOT, left ventricular outflow tract; RV, right ventricle.*

spine suggesting absence of the normally located superior caval vein (fig 1).

Cross sectional echocardiograms were available in four cases. In each case the left superior caval vein drained into a dilated coronary sinus which was visualised in parasternal and subcostal sections. In one case (case 2) the coronary sinus was so dilated that it looked like a tubular structure crossing the left atrial cavity above the mitral valve in the parasteral view (fig 2). A left superior caval vein and the bridging brachiocephalic vein were shown from the suprasternal notch in all cases. The connection of the left superior caval vein to the coronary sinus was not seen, but the dilated coronary sinus suggested such a connection. Contrast echocardiography was done in one case and proved the absence of a right superior caval vein and the connection of the persistent left superior caval vein to the coronary sinus.

Discussion

A persistent left superior caval vein draining into the coronary sinus is the most frequent type of systemic venous anomaly found when the atrial arrangement is normal; the abnormality is usually associated with a right superior caval vein in the normal position.[15] Rarely the persistent left superior caval vein drains into the left atrium; in this condition the coronary sinus may or may not be absent.[5,6] Raghib and associates described five cases in which the left superior caval vein terminated in the left atrium with atrial septal defect and absence of coronary sinus. These workers speculated that all these anomalies could have originated from a single anomalous developmental complex.[11]

The embryology of and anatomical variation in cases of a persistent left superior caval vein are discussed in detail elsewhere.[1,15,16] The origin of the left superior caval vein may be attributed to the persistence of the anterior cardinal vein with its caudal junction with the left duct of Cuvier. If, for unknown reasons, flow through the brachiocephalic vein is reversed and the right cephalic region drains into the left anterior cardinal vein an atretic or absent right superior caval vein will result.[4]

Although a persistent left superior caval vein draining into the right atrium by way of the coronary sinus has no significant haemodynamic effect, it is very important to know of its presence when a patient undergoes either open heart surgery with cardiopulmonary bypass, the Glenn procedure, Mustard's operation, or transvenous pacemaker insertion.[7–9,17] The problems which this abnormality may present and possible solutions have been reviewed.[3,10] When the persistent left superior caval vein drains into the left atrium, an intracardiac right to left shunt forms a part of the functional abnormality and cerebral complications may occur.[11] If this venous anomaly is associated with other intracardiac anomalies, preoperative diagnosis of the connection of the left superior caval vein to the left atrium is important, particularly in those congenital defects in which the right atrial pressure after operation tends to be higher than the left atrial pressure. An undetected left superior caval vein may result in a large residual right to left shunt, cyanosis, and suboptimal cardiac performance in the immediate postoperative period.

The diagnosis of a persistent left superior cava was usually made at cardiac catheterisation, at operation, or at necropsy. A persistent left superior caval vein may be suspected when the chest x ray shows an extra structure in the area of the aortic knob and upper mediastinum[1,16] but this is not a sensitive finding. Non-invasive diagnosis of systemic venous anomalies is possible by echocardiography.[14 18 19] The echocardiographic findings when there is a persistent connection between the left superior caval vein and the coronary sinus have been described.[20 21] M mode echocardiography shows an abnormal linear echo behind the mitral valve with a phasic movement similar to the aortic leaflet of the mitral valve. The cross sectional echocardiogram demonstrates a dilated coronary sinus on various views. Suprasternal echocardiography is very useful in delineating supracardiac anatomy. In the suprasternal paracoronal view the innominate vein and normally placed right superior caval vein are visualised with the right pulmonary artery and aorta. The left superior caval vein, when present, is seen apparently crossing the upper descending aorta, provided the latter is on the left, as the transducer is rotated and/or tilted to the left.[19] Direct echocardiographic diagnosis of absent right superior caval vein is also possible.[14 19] The connection of left superior caval vein to the heart is difficult to visualise directly, but it is usually predictable on the basis of associated findings.[14] When a clear suprasternal view is not available or there is any doubt, contrast echocardiography may be very helpful in confirming the venous connection to the heart.[18 22] Huhta and colleagues examined the sensitivity and specificity of echocardiography in diagnosing anomalous systemic venous return and concluded that cross sectional echocardiography was an extremely specific and highly sensitive method of recognising anomalous venous return.[14]

Absence of the right superior caval vein might well be expected to result in anomalous positioning of the sinoatrial node, which normally lies at the junction between the superior caval vein and right atrium. Half of our cases showed a superior leftwards deviation of the P wave axis; sinus slowing with junctional escape was detected in one case after open heart surgery. No case showed arrhythmia on a standard electrocardiogram before operation.

When a persistent left superior caval vein is present the electrocardiogram often shows an abnormal P wave axis and a normal or shortened P-R interval.[3 12 23] The mechanism of the leftwards deviation of the P wave axis is not clear. It has been attributed to the presence of an ectopic pacemaker around the coronary ostium,[12] but histological study clearly showed a normally placed sinoatrial node and absence of any pacemaker anywhere around the coronary ostium.[2 13] A geometric change of the left atrium may be a possible mechanism of left axis deviation of the P wave. Dilatation of the coronary sinus, which has to transmit all blood from the upper half of the body, may alter the geometry of the atrium and displace the left atrium upwards.[12] Besides the leftward deviation of the P wave axis, there have been reports of various arrhythmias in this anomaly.[9 13] James and colleagues made a detailed pathological study in two teenage boys with absent right superior caval vein. One died suddenly and the other died of arrhythmia 16 days after repair of ventricular septal defect. The first patient had a small sinus node and the second had a mass of polypoid tissue blocking the artery supplying the sinus node. In both the atrioventricular node was fragmented and stretched out over the large coronary sinus. They speculated that these histological abnormalities might be responsible for electrical instability of the heart and recommended detailed studies of the conduction system when there is a persistent left superior caval vein.[13]

Lenox and colleagues collected 11 cases of arrhythmia among published reports of 60 cases with absent right superior caval vein and suggested a possible predisposition to arrhythmia in this anomaly.[3] The same group recently reported on a pathological study on the conduction tissue in hearts with varying degrees of coronary sinus dilatation including four cases in which the right superior caval vein was absent.[2] They found that the size of the coronary sinus did not alter the histology of the adjacent conduction tissue. When the right superior caval vein was absent the sinoatrial node was normally placed and the atrioventricular conduction tissues were normal. But the sinoatrial node was hypoplastic in three out of four cases of absent right superior caval vein. They suggested that the development of atrioventricular nodal component is independent of the development of coronary sinus and that a hypoplastic sinoatrial node may predispose to the sick sinus syndrome. Although there have been reports of arrhythmia in cases of absent right superior caval vein, it is very difficult to know the true frequency of arrhythmia in these cases. It is even more difficult to ascertain the causal relation between arrhythmia and the occurrence of absent right superior caval vein. Hypoplasia of the sinoatrial node, however, suggests the possible development of sinus node dysfunction in this anomaly. If the true frequency of arrhythmia and the functional significance of hypoplastic sinoatrial node are to be determined long term follow up study and perhaps electrophysiological evaluation are needed.

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References

1 Winter FS. Persistent left superior vena cava; survey of world literature and report of thirty additional cases. *Angiology* 1954;5·90–132.

2 Lenox CC, Hashida Y, Anderson RH, Hubbard JD. Conduction tissue anomalies in absence of the right superior caval vein. *Int J Cardiol* 1985;8:251–60.

3 Lenox CC, Zuberbuhler JR, Park SC, *et al.* Absent right superior vena cava with persistent left superior vena cava: implications and management. *Am J Cardiol* 1980;45:117–22.

4 Garcia JM, Sanmarti J, Moller JH. Congenital absence of the right superior vena cava: report of two cases. *Eur J Cardiol* 1978;7:293–7.

5 Kabbani SS, Feldman M, Angelini P, Leachman RD, Cooley DA. Single (left) superior vena cava draining into the left atrium. *Ann Thorac Surg* 1973; **16** 518–25.

6 Sherafat M, Friedman S, Waldhausen JA. Persistent left superior vena cava draining into the left atrium with absent right superior vena cava. *Ann Thorac Surg* 1971;**11**·160–4.

7 Garcia JM. Absent right superior vena cava. *Am J Cardiol* 1980;**46**:714–5.

8 Harris A, Gialafos J, Jefferson K. Transvenous pacing in presence of anomalous venous return to heart. *Br Heart J* 1972;34:1189–91.

9 Camm AJ, Dymond D, Spurrell RAJ. Sinus node dysfunction associated with absence of right superior vena cava. *Br Heart J* 1979;41:504–7.

10 De Leval MR, Ritter DG, McGoon DC, Danielson GK. Anomalous systemic venous connection. Surgical considerations. *Mayo Clin Proc* 1975;**50**: 599–610.

11 Raghib G, Ruttenberg HD, Anderson RC, Amplatz K, Adams P Jr, Edwards JE. Termination of left superior vena cava in left atrium, atrial septal defect, and absence of coronary sinus. A developmental complex. *Circulation* 1965;31:906–18.

12 Momma K, Linde LM. Abnormal rhythms associated with persistent left superior vena cava. *Pediatr Res* 1969;3:210–6.

13 James TN, Marshall TK, Edwards JE Cardiac electrical instability in the presence of a left superior vena cava. *Circulation* 1976;54:689–97.

14 Huhta JC, Smallhorn JF, Macartney FJ, Anderson RH, de Leval M. Cross-sectional echocardiographic diagnosis of systemic venous return. *Br Heart J* 1982;48:388–403.

15 Campbell M, Deuchar DC. The left-sided superior vena cava. *Br Heart J* 1954;**16**:423–39.

16 Fraser RS, Drorkin J, Rossall RE, Eidem R. Left superior vena cava: a review of associated congenital heart lesions, catheterization data and roentgenologic findings. *Am J Med* 1961;**31**:711–6.

17 Garcia L, Levine RS, Kossowsky W, Lyon AF. Persistent left superior vena cava complicating pacemaker catheter insertion. *Chest* 1972;**61**:396–7.

18 Foale R, Bourdillon PD, Somerville J, Richards A. Anomalous systemic venous return: recognition by two-dimensional echocardiography. *Eur Heart J* 1983;4:186–95.

19 Snider AR, Silverman NH. Suprasternal notch echocardiography: a two-dimensional technique for evaluating congenital heart disease. *Circulation* 1981; **63**:165–73.

20 Hibi N, Fukui Y, Nishimura K, Miwa A, Kambe T, Sakamoto N. Cross-sectional echocardiographic study on persistent left superior vena cava. *Am Heart J* 1980;**100**:69–76.

21 Snider AR, Ports TA, Silverman NH. Venous anomalies of the coronary sinus: detection by M-mode, two-dimensional and contrast echocardiography. *Circulation* 1979;**60**:721–7.

22 Oguni H, Hatano T, Yamada T, *et al.* A case of absent right superior vena cava with persistent left superior vena cava: cross-sectional echocardiographic diagnosis. *Heart and Vessels* 1985;**1**:239–43.

23 Hancock EW. Coronary sinus rhythm in sinus venosus defect and persistent left superior vena cava. *Am J Cardiol* 1964;**14**:608–15.

Br Heart J 1987;57:479–82

Case reports

Percutaneous balloon dilatation in congenital mitral stenosis

LUIS E ALDAY, ERNESTO JUANEDA

From the Department of Cardiology, Children's Hospital, and the Department of Paediatrics, National University of Cordoba, Cordoba, Argentina

SUMMARY A three year old girl with severe congenital mitral stenosis was successfully treated by percutaneous balloon dilatation of the mitral valve. Cardiac catheterisation and cross sectional and Doppler echocardiography indicated that the orifice of the mitral valve had doubled in area. A small atrial septal defect was found at follow up cardiac catheterisation and angiography.

Balloon dilatation of the mitral valve is a reasonable alternative to surgical treatment for typical congenital mitral stenosis even in young children.

Since Kan *et al* first advocated the use of percutaneous balloon dilatation for the treatment of congenital pulmonary valve stenosis,[1] the procedure has been widely applied in this[2-4] and in other obstructive lesions such as aortic valve stenosis,[5] coarctation of the aorta,[6] peripheral pulmonary stenoses,[7] and obstructed veins.[8] Balloon angioplasty has also been successful as a treatment for rheumatic mitral valve stenosis in older children, young adults, and adults.[9-12] The technique was also used in an adolescent with congenital mitral valve stenosis.[13] We report a case of successful dilatation of the mitral valve by percutaneous balloon dilatation in a young child.

Case report

A girl aged 3 years and 4 months with a history of poor exercise tolerance and failure to thrive was referred for cardiac evaluation and treatment. On physical examination she was undernourished (weight 8·5 kg, below the third percentile) and the findings at auscultation were typical of severe mitral stenosis. The rest of the physical examination was unremarkable. Chest *x* rays showed moderate cardiomegaly with a cardiothoracic ratio of 0·58. There was left atrial and right ventricular enlargement and signs of pulmonary venous hypertension. The electrocardiogram had a mean QRS axis of +100° in the frontal plane and there was evidence of left atrial enlargement and right ventricular hypertrophy. Cross sectional echocardiographic and Doppler examination revealed mitral stenosis with a valve area of 1 10 cm^2. After obtaining informed consent from the parents, we performed combined percutaneous cardiac catheterisation and selective cineangiocardiography followed by mitral valve dilatation from the right femoral vein and the left femoral artery under general anaesthesia. The haemodynamic findings showed moderately severe pulmonary hypertension and a 7 mm Hg gradient across the mitral valve (table). The left ventricular cineangiogram disclosed severe mitral stenosis and slight mitral incompetence. Mild tricuspid regurgitation and considerable enlargement of the left atrium with a prolonged washout time in the laevophase were seen on right ventricular cineangiography.

We used the following technique for the mitral valve dilatation. The venous catheter was replaced by a number 8·5 French transseptal left heart catheter (USCI) which was advanced to the right atrium. A Brockenbrough needle was introduced into the catheter and the atrial septum was punctured. The catheter was advanced over the needle into the left atrium and the needle was withdrawn. We then gave 100 units of heparin per kg. After the left atrial pressure had been measured the catheter was advanced

Requests for reprints to Dr Luis E Alday, Department of Cardiology, Hospital de Niños, Corrientes 643, 5000 Cordoba, Argentina.

Table *Cardiac catheterisation data before, immediately after, and one month after mitral angioplasty*

	Before	*After*	*1 month*
Right atrium (mm Hg)	(5)	(8)	(2)
Right ventricle (mm Hg)	65/4	66/7	51/4
Pulmonary artery (mm Hg)	65/35 (45)	—	48/12 (24)
Left atrium (mm Hg)	(16)	(10·5)	(6·5)
Left ventricle (mm Hg)	85/9	105/9	105/3·5
Aorta (mm Hg)	85/45 (65)	100/50 (72)	105/70 (82)
Qp (l/min/m²)	5·2	—	6·7
Qs (l/min/m²)	5·2	—	4·1
Qp : Qs ratio	1·0 : 1·0	—	1·6 : 1·0
Rp (u/m²)*	8·6	—	3·6
Rs (u/m²)*	11·5	—	19·5
Rp : Rs ratio	0·7 : 1·0	—	0·2 : 1·0
Mitral valve area (cm²)	0·59	—	1·22

Numbers in parentheses are mean pressures. Qp, pulmonary flow; Qs, systemic flow; Rp, total pulmonary resistance; Rs, systemic resistance. * Wood units.

through the mitral valve into the left ventricle. A 0·038 inch Teflon coated guide wire (180 cm long) (Cook) was then placed in the left ventricle through the transseptal catheter. The guide wire was looped within the ventricular cavity and advanced through the aortic valve to the ascending aorta. The transseptal catheter was removed and a 12 mm balloon angioplasty catheter number 9 French (Medi-Tech)

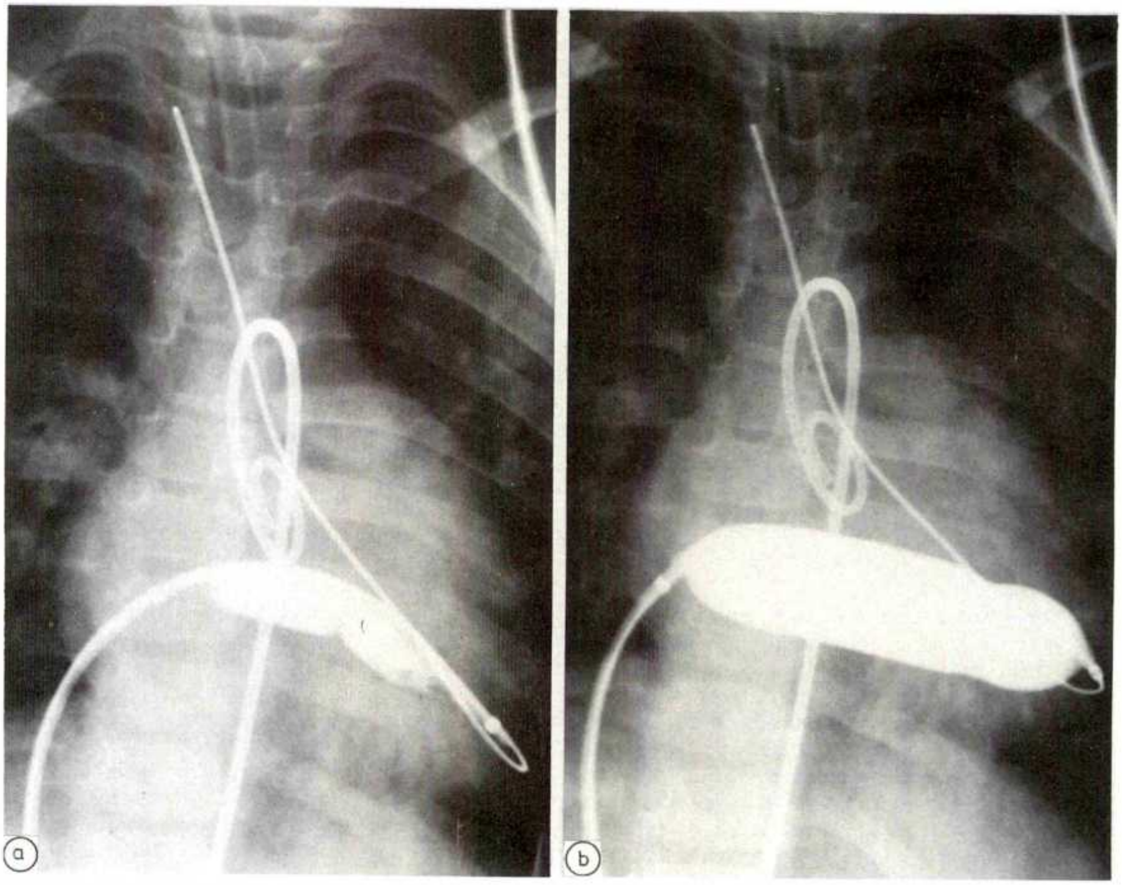

Fig 1 *(a) X ray of the 12 mm balloon catheter placed across the mitral orifice half inflated and showing an indentation in the area of the stenotic mitral valve. (b) X ray of the 18 mm balloon catheter distended at full pressure.*

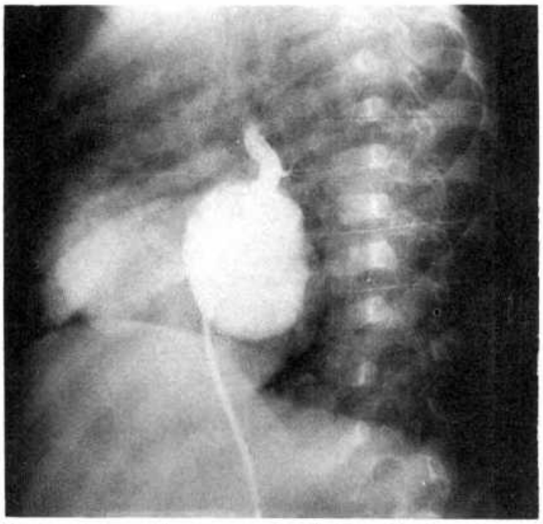

Fig 2 *Left atrial angiogram in the four chamber view showing an enlarged left atrium and a small atrial septal defect.*

was advanced over the guide wire and placed across the mitral valve orifice (fig 1a). The balloon was then inflated with diluted contrast medium at 354 kN/m^2 (3·5 atm) pressure for three 10 second periods. The procedure was repeated with an 18 mm angioplasty catheter (fig 1b). After the balloon catheter had been removed, the transseptal catheter was reintroduced and the pressure measurements were repeated (table). The arterial catheter, which had been left at aortic valve level for continuous recording of systemic pressure, was passed in the left ventricle and cineangiography was repeated.

After balloon dilatation the transmitral valve gradient decreased to 1·5 mm Hg. The left ventricular cineangiogram showed mild mitral regurgitation equivalent to that found at the previous angiographic examination. The whole procedure took one hour and 40 minutes and there were no complications. The patient was discharged from hospital two days later.

Physical examination after dilatation disclosed a much softer mid-diastolic rumble in the area of the mitral valve. There had been no murmur immediately after dilatation. Cross sectional and Doppler echocardiographic examinations were repeated a week later and they indicated an increase of the mitral valve orifice to 2·34 cm^2. At follow up the patient's exercise tolerance was considerably improved. Cardiac catheterisation performed a month after angioplasty showed a decline in pulmonary artery pressure and resistance and a 3 mm Hg transmitral gradient (table). The mitral valve area had apparently doubled and there was evidence of a small atrial septal defect both by oximetry and by left atrial cineangiography (fig 2).

Discussion

Balloon dilatation of the mitral valve is an effective method for relieving stenosis of the rheumatic mitral valve.[9–12] It has been used in older children and adults and even in elderly patients with calcific mitral stenosis[14 15]; no serious complications have been reported. When balloon angioplasty of the mitral valve was attempted in two patients with congenital mitral stenosis it was successful in the adolescent patient but failed in the 2 year old boy who also had associated anomalies.[13]

Despite the small size of our patient, balloon dilatation of the stenotic mitral valve was achieved without complication and the procedure was not lengthy. Haemodynamic measurements and echocardiography and Doppler studies both showed that the mitral valve orifice had doubled in area after dilatation.

The technique we used differed only slightly from that described by Lock *et al* and Kveselis *et al*.[9 13] As reported by Lock *et al*,[9] the distal end of the exchange guide wire was placed in the ascending aorta to facilitate replacement of the catheter. We did not use a Swan-Ganz catheter to traverse the aortic valve, however; we accomplished this objective by looping the guide wire within the left ventricle. A 12 mm balloon catheter was used to facilitate the subsequent passage of the larger 18 mm balloon across the atrial septum. As was also seen in one of Lock's patients,[9] we found a small residual atrial septal defect at follow up catheterisation. Nevertheless, there was clinical and haemodynamic improvement after dilatation. To avoid creating an atrial septal defect after transseptal mitral valve dilatation, Babic *et al* performed mitral dilatation by introducing the balloon catheter from the arterial side.[12] All their patients were adults, however, and it is unlikely that this technique could be applied in young children.

Congenital mitral stenosis accounts for only 0·2% of all congenital heart defects.[16] Four anatomical types have been described.[17] Typical mitral stenosis is found in nearly 50% of patients. In this type the leaflets are thickened and are fused and the chordae shortened. Other types are mitral stenosis as a component of the hypoplastic left heart syndrome, the supravalvar mitral ring, and the parachute mitral valve. We think that for typical mitral stenosis balloon dilatation is a reasonable alternative to surgical treatment, even in young children.

References

1 Kan JS, White RI Jr, Mitchell SE, Gardner TJ. Percutaneous balloon valvuloplasty: a new method for treating congenital pulmonary valve stenosis. *N Engl J Med* 1982;**307**.540–2.

2 Lababidi Z, Wu J. Percutaneous balloon valvuloplasty. *Am J Cardiol* 1983;**52**:560–2.

3 Rocchini AP, Kveselis DA, Crowley D, Dick M, Rosenthal A. Percutaneous balloon valvuloplasty for treatment of congenital pulmonary valve stenosis in children. *J Am Coll Cardiol* 1984;**3**:1005–12.

4 Tynan M, Baker EJ, Rohmer J, *et al*. Percutaneous balloon pulmonary valvuloplasty. *Br Heart J* 1985; **53**:520–4.

5 Lababidi Z, Wu JR, Walls TJ. Percutaneous balloon aortic valvuloplasty; results in 23 patients. *Am J Cardiol* 1984;**53**·194–7.

6 Lock JE, Bass JL, Amplatz K, Fuhrman BP, Castaneda-Zuniga WR. Balloon dilatation angioplasty of coarctations in infants and children. *Circulation* 1983;**68**:109–16.

7 Lock JE, Castaneda-Zuniga WR, Fuhrman BP, Bass JL. Balloon dilatation angioplasty of hypoplastic and stenotic pulmonary arteries. *Circulation* 1983;**67**: 962–7.

8 Lock JE, Bass JL, Castaneda-Zuniga W, Fuhrman BP, Rashkind WJ, Lucas RV Jr. Dilation angioplasty of congenital or operative narrowing of venous channels. *Circulation* 1984;**70**:457–64.

9 Lock JE, Khalilullah M, Shrivastava S, Bahl V, Keane JF. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. *N Engl J Med* 1985;**313**:1515–8.

10 Inowe K, Owaki T, Nakamura T, Kitamura F, Miyamoto N. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. *J Thorac Cardiovasc Surg* 1984;**87**:394–402.

11 Zaibag MA, Ribeiro PA, Kasab SA, Faghi MRA. Percutaneous double-balloon mitral valvotomy for rheumatic mitral valve stenosis. *Lancet* 1986;**i**: 757–61.

12 Babic UU, Pejcic P, Djurisic Z, Vucinic M, Grujicic SM. Percutaneous transarterial balloon valvuloplasty for mitral valve stenosis. *Am J Cardiol* 1986;**57**: 1101–4.

13 Kveselis DA, Rocchini AP, Beekman R, *et al*. Balloon angioplasty for congenital and rheumatic mitral stenosis. *Am J Cardiol* 1986;**57**:348–50.

14 McKay RG, Lock JE, Keane JF, Safian RD, Aroesty JM, Grossman W. Percutaneous mitral valvuloplasty in an adult patient with calcific rheumatic mitral stenosis. *J Am Coll Cardiol* 1986;**7**:1410–5.

15 Palacios IF, Lock JE, Keane JF, Block PC. Percutaneous transvenous balloon valvotomy in a patient with severe calcific mitral stenosis. *J Am Coll Cardiol* 1986;**7**:1416–9.

16 Keith JD. Prevalence, incidence and epidemiology. In: Keith JD, Rowe RD, Vlad P. *Heart disease in infancy and childhood*. New York: Macmillan, 1978:6.

17 Ruckman RN, Van Praagh R. Anatomic types of congenital mitral stenosis: report of 49 autopsy cases with considerations of diagnostic and surgical implications. *Am J Cardiol* 1978;**42**:592–601.

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Aortic atresia with complete transposition

ROXY N S LO, K C LAU, M AUNG-KHIN*

*From the Department of Paediatrics, University of Hong Kong; and the *Department of Pathology, Grantham Hospital, Hong Kong*

SUMMARY Aortic atresia with ventriculoarterial discordance in a three day old neonate was studied by cross sectional echocardiography and the anatomy was confirmed at necropsy.

Aortic atresia with hypoplasia of the ascending aorta and left ventricle nearly always occurs with atrioventricular and ventriculoarterial concordant connections and normally related great arteries.[1 2] Its association with complete transposition of great arteries has been reported only once in a six year old girl studied by cardiac catheterisation.[3] We report the cross sectional echocardiographic and postmortem findings of a neonate with this rare condition.

Case report

A three day old Chinese female baby was referred because of poor feeding and cyanosis. She was the second child of healthy non-consanguineous parents. The antenatal history was uneventful and there were no early perinatal problems. She weighed 3010 g at birth and had no external malformations. Examination revealed a blue tinge to the skin which increased when she cried and mild dyspnoea with a respiratory rate of 55 breaths per minute. The pulses were weak with a rate of 150 beats per minute and a pressure of 80/60 mm Hg in all limbs. The precordium was hyperactive with a biventricular impulse and the apex beat was displaced to the left midaxillary line. Auscultation showed a loud single second heart sound and a soft grade 2/6 ejection systolic murmur over the upper left sternal border. The lungs were clear and the liver was palpable 3 cm below the right costal margin. A chest *x* ray showed a cardiothoracic ratio of 0·68 and markedly plethoric lungs. The electrocardiogram showed evidence of right atrial and left ventricular hypertrophy with absence of the R wave in the right precordial leads; the mean QRS axis was 45°. Arterial oxygen partial pressure in room air was 5·15 kPa and rose to 11·29 kPa after breathing 100% oxygen.

Cross sectional echocardiography was performed with an Advanced Technology Laboratory Mk600 Duplex system machine mounted with a 5 MHz mechanical sector transducer. Standard precordial, subcostal, and suprasternal views were taken.

There was the usual atrial arrangement and a concordant atrioventricular connection. The anterior right sided ventricle was small and had a hypoplastic though patent tricuspid valve with attachments to the interventricular septum (fig 1a). The posterior ventricle was large, smooth walled, and contained two papillary muscles with a bicuspid mitral valve. No ventricular septal defect could be identified. The pulmonary trunk arose from the posterior ventricle and was connected via a large ductus arteriosus to the descending aorta. The ascending aorta was not readily visible from the parasternal long axis view. It could be demonstrated from the apical four chamber projection by clockwise rotation of the transducer (fig 1b) and also from the high parasternal short axis view by rotating the transducer counterclockwise and tilting it towards the right shoulder; it was a small tubular structure running to the right and in front of the pulmonary artery (fig 1c). Its presumed connection with the right ventricle, however, could not be well demonstrated. The hypoplastic aorta was also clearly seen from the suprasternal notch view.

A Doppler flow study with the sample volume placed in the ascending aorta showed that during systole there was retrograde flow from the aortic arch towards the aortic root while during diastole flow was away from the ascending aorta (fig 1d).

Cardiac catheterisation was planned but was postponed because the baby developed diarrhoea after admission. On day 8 she became increasingly dyspnoeic with wet lungs and gallop rhythm. Repeat echocardiography showed progressive deterioration of left ventricular contractions while the ductus re-

Requests for reprints to Dr Roxy N S Lo, Department of Paediatrics, University of Hong Kong, The Grantham Hospital, 125 Wong Chuk Hang Road, Aberdeen, Hong Kong.

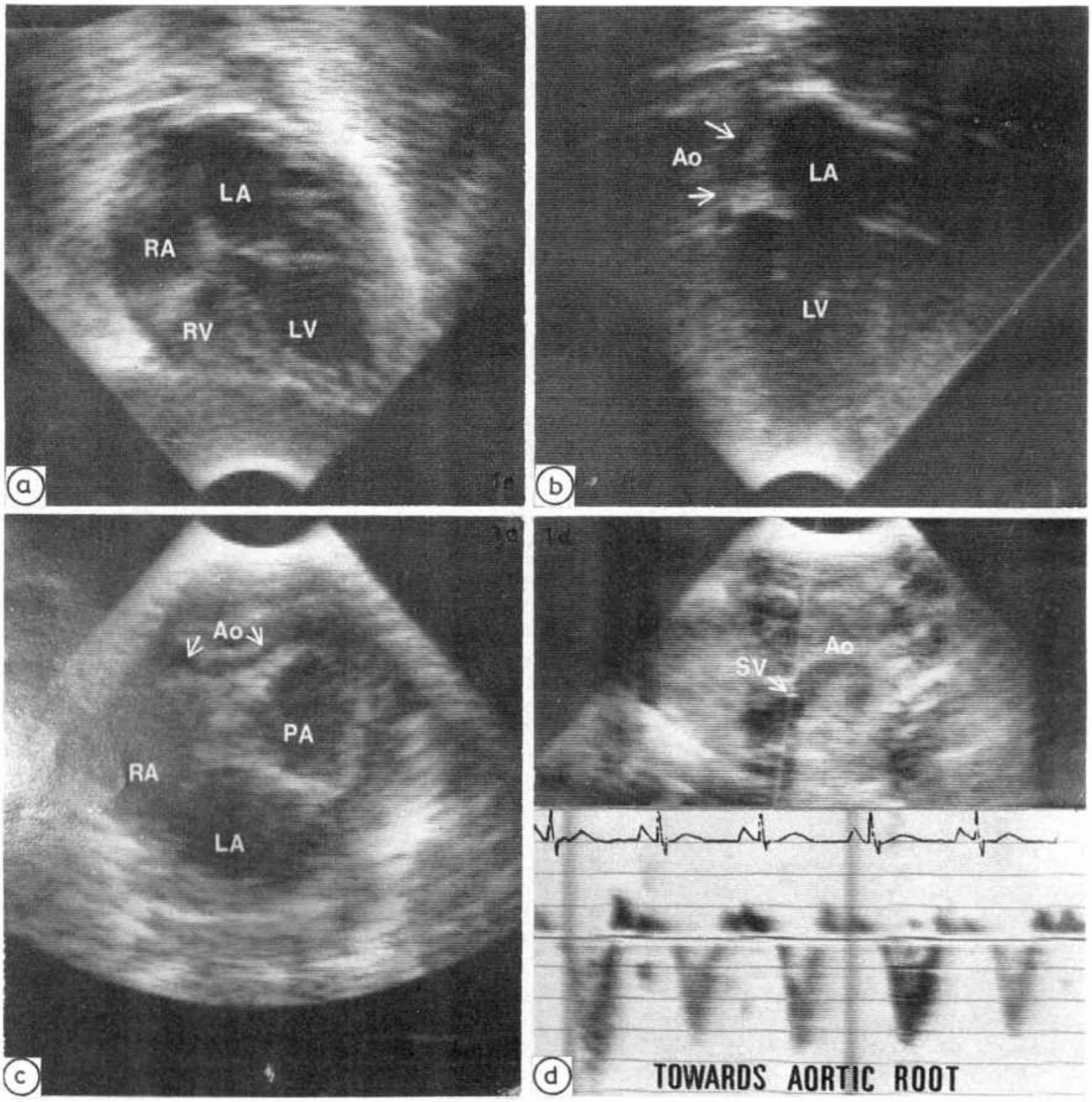

Fig 1 *Cross sectional echocardiographic views. (a) Four chamber view showing the hypoplastic right ventricle and tricuspid valve. (b) Apical long axis and (c) high parasternal short axis view showing the hypoplastic ascending aorta. Its connection with the heart was not demonstrated. (d) Suprasternal notch view of the hypoplastic ascending aorta. Doppler flow pattern with the sample volume (SV) in the ascending aorta showed flow towards the aortic root during systole and away from it in diastole. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; Ao, aorta; PA, pulmonary artery.*

mained widely patent. Despite active measures she finally succumbed to refractory heart failure when she was 10 days old.

NECROPSY FINDINGS

The heart was large and weighed 67 grams. There was the usual atrial arrangement. The cardiac apex was directed to the left and the systemic and pulmonary veins drained normally to the right and left atrial chambers respectively. No definite interventricular groove was present on the surface of the heart, but the distribution of coronary arteries

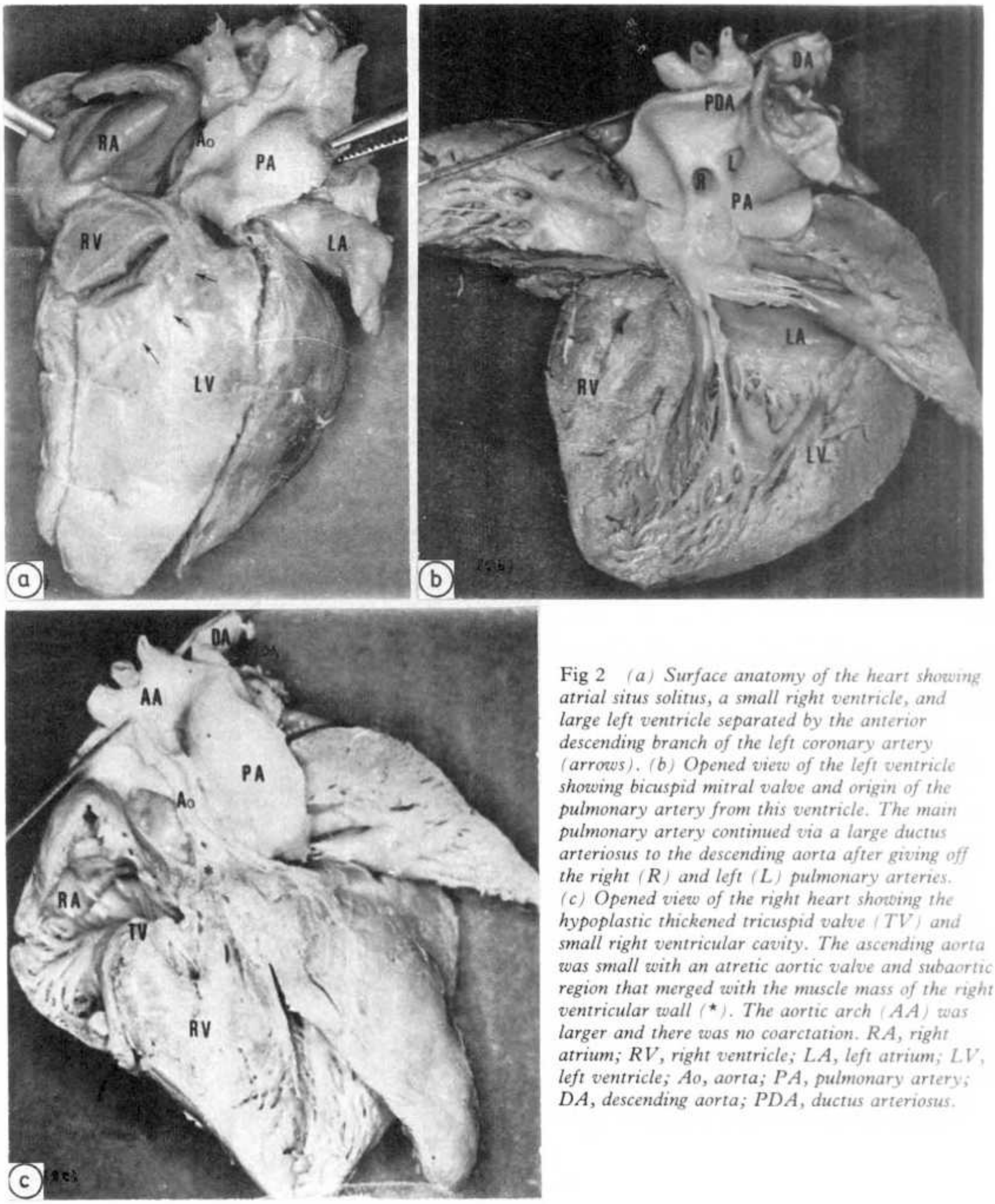

Fig 2 *(a) Surface anatomy of the heart showing atrial situs solitus, a small right ventricle, and large left ventricle separated by the anterior descending branch of the left coronary artery (arrows). (b) Opened view of the left ventricle showing bicuspid mitral valve and origin of the pulmonary artery from this ventricle. The main pulmonary artery continued via a large ductus arteriosus to the descending aorta after giving off the right (R) and left (L) pulmonary arteries. (c) Opened view of the right heart showing the hypoplastic thickened tricuspid valve (TV) and small right ventricular cavity. The ascending aorta was small with an atretic aortic valve and subaortic region that merged with the muscle mass of the right ventricular wall (*). The aortic arch (AA) was larger and there was no coarctation. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; Ao, aorta; PA, pulmonary artery; DA, descending aorta; PDA, ductus arteriosus.*

indicated a small right and a large left ventricle (fig 2a). The internal appearance of the atria was normal and the foramen ovale was patent. The left atrium was connected by a bicuspid mitral valve to the main ventricular chamber which had the morphological characteristics of a left ventricle (fig 2b). The pulmonary trunk originated from the left ventricle and was connected via a large ductus arteriosus to the descending aorta after giving rise to the right and left pulmonary arteries. The right atrium was connected via a stenotic and hypoplastic tricuspid valve to a small right ventricle which was present as a tiny cavity within the thick muscle mass on the right shoulder of the left ventricle (fig 2c). No right ventricular outflow tract could be identified. The aortic valve and subaortic region were atretic and merged with the muscle mass of the right ventricle. The ascending aorta was 2 mm in diameter and there were two coronary arteries present in the usual positions. The aortic arch was larger and gave rise to normal brachiocephalic arteries.

Discussion

Aortic atresia with ventriculoarterial discordance is a rare congential malformation of the heart. We found only six cases reported in published reports. Three were associated with double inlet univentricular atrioventricular connection with main chamber of left ventricular morphology, one with corrected transposition, and one with absent tricuspid valve and atrioventricular discordance.[4] McGarry *et al* described the only patient with aortic atresia occurring with complete transposition of the great arteries diagnosed by angiography; this patient was alive at the age of six.[3] As in our patient, the clinical picture was dominated by heart failure with mild cyanosis. Physical examination showed cardiomegaly with a single second heart and non-specific murmurs. The electrocardiogram showed characteristically right atrial and left ventricular hypertrophy rather than right ventricular hypertrophy as seen in the usual hypoplastic left heart syndrome. Definitive diagnosis required further investigations such as cardiac catheterisation, and in our case non-invasive examination by cross sectional echocardiography.

A morphologically left ventricle is considered to be more effective than a right ventricle as the supporting chamber for the systemic and pulmonary circulations and led to the long survival of McGarry's patient.[3] Theoretically a morphologically left ventricle should also provide a more normal physiological state.[5] The early death of our patient despite the patency of the ductus arteriosus could be the result of insufficient coronary artery perfusion. Our Doppler study showed retrograde flow via the small ascending aorta that was present only during systole, while during diastole there was negative flow attributed to the low vascular resistance in the pulmonary vessles.[6] Coronary insufficiency, together with volume overloading of the systemic ventricle, rather than ductal closure may be the major cause of death in patients with aortic atresia because the ductus arteriosus was found to be widely patent in most patients.[1 2]

References

1 Bharati S, Lev M. The surgical anatomy of hypoplasia of aortic tract complex. *J Thorac Cardiovasc Surg* 1984;88:97–101.

2 Anderson RH, Ho SY, Zuberbuhler JR, Moulton AL, Gerlis LM. Surgery for hypoplastic left heart. Surgical anatomy and definitions. In: Marcelletti C, Anderson RH, Becker AE, *et al*, eds. *Paediatric cardiology*. Vol. 6. London: Churchill Livingstone, 1986:111–21.

3 McGarry KM, Taylor JFN, Macartney FJ. Aortic atresia occurring with complete transposition of great arteries. *Br Heart J* 1980;44:711–3.

4 Bullaboy CA, Harned HS Jr Aortic atresia with double inlet left ventricle, rudimentary left sided right ventricle, and ventriculoarterial discordance. *Br Heart J* 1984;52:349–51.

5 Castaneda AR, Norwood WI. Surgery for hypoplastic left heart. Surgical considerations. In: Marcelletti C, Anderson RH, Becker AE, *et al*, eds. *Paediatric cardiology*. Vol. 6. London: Churchill Livingstone, 1986:127–34.

6 Freedom RM, Culham JAC, Moes CAF, Harrington DP. Selective aortic root angiography in the hypoplastic left heart syndrome. *Eur J Cardiol* 1976;4: 25–9.

Br Heart J 1987;57:487–9

Neurogenic hypertension associated with an excessively high excretion rate of catecholamine metabolites

CHRISTIAN FUNCK-BRENTANO,* JEAN-YVES PAGNY, JOËL MENARD

From Service d'Hypertension Artérielle et de Médecine Interne, Hôpital Broussais, Paris, France

SUMMARY A 60 year old hypertensive patient suffered several cerebral infarctions. A phaeochromocytoma was suspected because the excretion rates of vanillylmandelic acid and its methoxy derivatives were raised and the patient had hypertensive crises. No tumour was found, however, by ^{131m}I-iodobenzylguanidine scintigraphy and computed tomography of the abdomen. Moreover, the enhanced orthostatic plasma catecholamine response suggested that the high excretion rates of catecholamine metabolites were more likely to be caused by the syndrome of raised catecholamines after cerebrovascular accidents than a phaeochromocytoma.

A phaeochromocytoma should not be diagnosed within several months of cerebral infarction without first excluding the possibility of a hyperadrenergic state induced by cerebral infarction.

Hypertension associated with increased excretion of catecholamines has been described in several conditions that simulate phaeochromocytoma.[1 2] We describe a hypertensive patient who had several cerebral infarctions and excessively high excretion rates of catecholamine metabolites that persisted for several months. Phaeochromocytoma, whether adrenal or ectopic, was not demonstrated despite the use of specific and sensitive diagnostic techniques. An excessive increase in plasma catecholamine concentration in response to standing up suggested a non-tumoral pattern that was consistent with a neurogenic hyperadrenergic state.

Case report

A 60 year old man was referred to our hospital on 2 December 1984 with severe resistant hypertension and a high excretion rate of catecholamine metabolites. He had a two year history of asymptomatic untreated hypertension with no other relevant medical or surgical history. On 4 October 1984 right facial palsy with dysarthria developed suddenly and he was admitted to another hospital. Fluctuating high blood pressure was found. Examination disclosed a mild right hemiparesia without sensory loss. Clinical examination was otherwise normal. Standard laboratory values were normal. An electrocardiogram disclosed typical signs of left ventricular hypertrophy and normal sinus rhythm. A chest radiograph showed mild cardiomegaly but no mediastinal tumour. Intravenous digitised cervical angiography showed major atherosclerotic lesions of both vertebral arteries without obstruction. The urinary excretion rate of catecholamine metabolites was measured 10 days after admission.[3] It gave the following results: vanillylmandelic acid 6·21 mg (31·3 μmol)/24 h (normal < 8 mg (40·4 μmol)/24 h); metanephrine and normetanephrine 1407 μg (normal < 700 μg)/24 h; normetanephrine 972 μg (5·3 μmol)/24 h.

Blood pressure remained unstable despite the administration of several antihypertensive drugs (figure). Excretion rates of catecholamine metabolites remained raised and concentrations of normetanephrine predominated over those of metanephrine. The excretion rate of vanillylmandelic acid reached 11·8 mg/24 h (59·5 μmol/24h) on 16 November 1984. On 28 November the patient had a left hemiparesis that spared his face.

At admission the patient was drowsy. Supine blood pressure was 214/108 mm Hg and the pulse

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*Present address: Dr Christian Funck-Brentano, Department of Pharmacology—Room AA 3228, Medical Center North, Vanderbilt University, Nashville, TN 37232, USA.

Reprints will not be available from the authors.

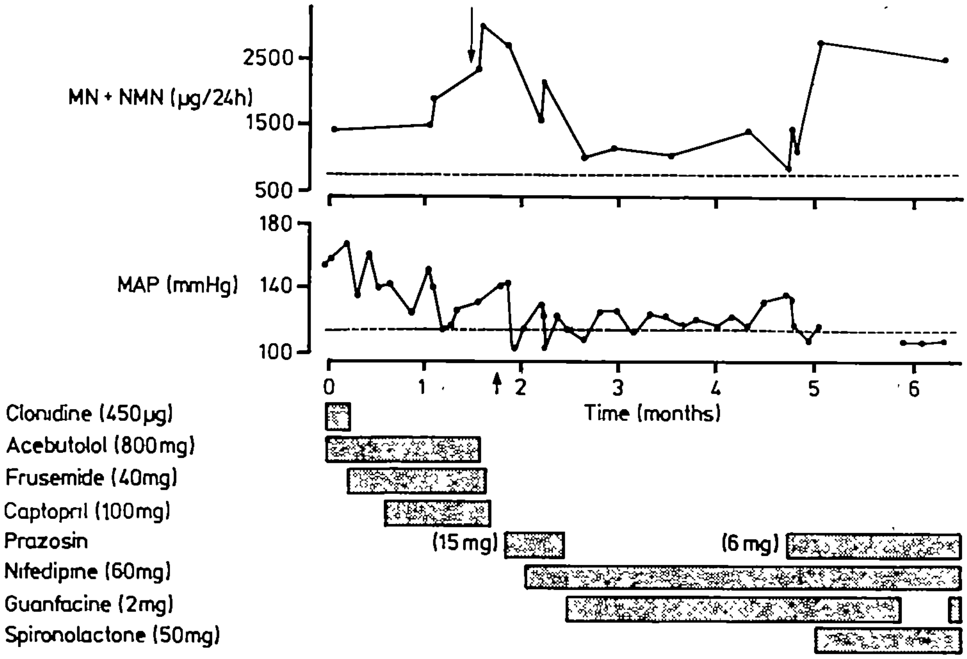

Figure *Clinical course of the patient. Broken lines represent the upper limit for normal values. The small arrow indicates the time the patient had his second cerebral infarction. The large arrow indicates the time of admission to our hospital. Daily dosage of antihypertensive drugs is indicated. MAP, mean arterial pressure. Values are the means of two or three daily supine blood pressure measurements; MN + NMN, metanephrine + normetanephrine. MN 1 µmol = 197·23 µg; NMN 1 µmol = 183·20 µg.*

rate was 66 beats/minute. He did not have a history of headache, excessive sweating, or palpitation. Neurological examination revealed a mild left sided pure motor deficit sparing the face, fluctuating consciousness, and frequent yawns. Clinical examination was otherwise normal. Lumbar puncture yielded a sample of normal cerebrospinal fluid. A cerebral computed tomogram revealed multiple areas of reduced density. The blood pressure continued to fluctuate, with supine systolic pressure ranging from 140 to 250 mmHg. Blood pressure peaks were not accompanied by headache, sweating, or tachycardia. Irrespective of the treatment the patient was taking, there was a mean drop of systolic and diastolic blood pressure of 25 and 10 mmHg respectively and a concomitant 30% average increase of heart rate when he stood up. Micturition did not induce headache, sweating, tachycardia, or variation in blood pressure. The results of intravenous pyelography were normal. A computed tomogram of the adrenal glands did not show a tumour. Whole body ^{131m}I-iodobenzylguanidine scintigraphy, which included the head, did not show any abnormal uptake. Urinary bladder uptake revealed no important abnormality.

The excretion rate of catecholamine metabolites (metanephrine, normetanephrine, vanillylmandelic acid) reached a peak three days after the occurrence of the left hemiparesis and remained raised during the next three months. Then a second rise occurred (figure). The specificity of the urinary determinations was borne out by the results of high performance liquid chromatography. An oral dose of 1 mg of prazosin produced a maximum drop of 4% in arterial blood pressure during a seven hour follow up.

Four and a half months after admission, 10 days after the withdrawal of guanfacine and while the patient was taking prazosin, nifedipine, and spironolactone, we measured plasma catecholamine concentrations while he was supine and after standing up.[4] The following results were obtained: noradrenaline 5661 pg/ml (33·5 pmol/ml) supine and 11796 pg/ml (69·7 pmol/ml) after standing for five minutes (normal supine < 355 pg/ml (2·1 pmol/ml)); adrenaline 162 pg/ml (0·88 pmol/ml) supine and 287 pg/ml (1·57 pmol/ml) after standing for five minutes (normal supine < 85 pg/l (0·46 pmol/ml)). Neurological examination was consistent with a so-called pseudobulbar palsy.

Discussion

This case emphasises the difficulty in distinguishing between phaeochromocytoma and cerebrovascular accidents causing raised concentrations of catecholamines. In hypertensive patients with raised excretion rates of catecholamine metabolites, the diagnosis of true (tumoral) phaeochromocytoma is suggested by several features. These are the triad of headache, sweating attacks, and palpitation. When this triad is absent, the probability of phaeochromocytoma is <1 in 1000.[5] A prolonged (75 h) fall in blood pressure after the administration of prazosin is also suggestive of phaeochromocytoma.[6] Crises precipitated by micturition have been described in patients with bladder phaeochromocytoma.[7]

Computed tomography can detect small tumours and is particularly useful for the diagnosis of ectopic tumours when these are indicated by scintigraphy or venous concentrations of catecholamines. The diagnosis and localisation of adrenal and extra-adrenal phaeochromocytomas has been improved by the use of ^{131m}I-iodobenzylguanidine scintigraphy, which has a sensitivity of 89% and a specificity of 95% for the diagnosis of true phaeochromocytomas.[8]

Plasma and urine catecholamine concentrations also help to distinguish between true phaeochromocytomas and the syndrome of raised catecholamines. Raised urinary concentrations of adrenaline usually indicate an intra-adrenal tumour; however, there are reports of false negative results.[8] It has been suggested that a plasma adrenaline concentration of <200 pg/ml (1·1 nmol/l) associated with a noradrenaline plasma concentration less than twice the upper limit of normal indicates a non-tumoral cause for the hyperadrenergic state.[9] The most important features in patients with phaeochromocytoma are the lack of an increase in plasma catecholamines in response to standing[10] and the lack of a decrease in plasma catecholamine concentrations after pentolinium[9] or clonidine.[11] When ^{131m}I-iodobenzylguanidine scintigraphy is negative but plasma catecholamine concentrations indicate the presence of a phaeochromocytoma, selective venous sampling of catecholamines is invaluable in determining the sources of the excess catecholamines.[12] This technique requires considerable radiological skill and expert assay facilities, however.

Cerebral infarction can increase total catecholamine concentrations in the peripheral venous plasma of hypertensive patients,[13] and catecholamine urinary excretion rates.[14] Stoica *et al* found that urinary noradrenaline excretion increased in the first week after cerebral infarction in 46 patients, whereas it was normal thereafter. The excretion rate of vanillylmandelic acid was normal during the first month.[14] We believe that the clinical, biological, and radiological picture in our patient rules out the presence of a phaeochromocytoma and suggests a hyperadrenergic state induced by cerebral infarction.

In hypertensive patients with high catecholamine excretion rates after cerebral infarction, ^{131m}I-iodobenzylguanidine scintigraphy and plasma catecholamine response to standing or suppression tests are most useful in distinguishing between a true phaeochromocytoma and the syndrome of raised catecholamines. Because blood pressure control was only achieved in our patient after administration of guanfacine and prazosin we suggest that hypertensive patients with high excretion rates of catecholamines after cerebral infarction should be treated with peripheral α_1 blocking agents and/or centrally acting α_2 agonists.

We thank Dr Etienne Comoy for measuring the plasma catecholamine concentrations.

References

1 Kuchel O Pseudopheochromocytoma *Hypertension* 1985;7 151–8.
2 Mazey RM, Kotchen TA, Ernst CB. A syndrome resembling pheochromocytoma following a stroke. Report of a case. *JAMA* 1974,230:575–7
3 Anton AH, Sayre DF Distribution of metanephrine and normetanephrine in various animals and their analysis in diverse biological material. *J Pharmacol Exp Ther* 1966;153.15–29.
4 Da Prada M, Zurcher G. Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range. *Life Sci* 1976,19.1161–74
5 Plouin P-F, Degoulet P, Tugaye A, Ducrocq M-B, Menard J. Le depistage du pheochromcytome: chez quels hypertendus? Etude semiologique chez 2585 hypertendus dont 11 ayant un pheocyromocytome *Nouv Presse Med* 1981,10 869–72.
6 Wallace JM, Gill DP Prazosin in the diagnosis and treatment of pheochromocytoma. *JAMA* 1978,240:2752–3.
7 Schutz W, Vogel E Pheochromocytoma of the urinary bladder A case report and review of the literature. *Urol Int* 1984;39 250–5.
8 Ackery DM, Tippett PA, Condon BR, Sutton HE, Wyeth P New approach to the localisation of phaeochromocytoma: imaging with iodine-131-meta-iodobenzylguanidine *Br Med J* 1984,288.1587–91.
9 Brown MJ, Allison DJ, Jenner DA, Lewis PJ, Dollery CT Increased sensitivity and accuracy of phaeochromocytoma diagnosis achieved by the use of plasma-adrenaline estimations and a pentolinium-suppression test *Lancet* 1981,i:174–7
10 Newsome HH Jr. The lack of normal catecholamine responses in patients with pheochromocytomas. *Surgery* 1983,94 932–7
11 Bravo EL, Tarazi RC, Fouad FN, Vidt DG, Gifford RW Jr. Clonidine suppression test. A useful aid in the diagnosis of pheochromocytoma. *N Engl J Med* 1981;305·623–6.
12 Brown MJ, Allison DJ Apologia for older techniques for localising phaeochromocytoma [Letter]. *Lancet* 1984;ii 1274.
13 Meyer JS, Stoica E, Pascu I, Shimazu K, Hartmann A Catecholamine concentrations in CSF and plasma of patients with cerebral infarction and haemorrhage. *Brain* 1973;96·277–88.
14 Stoica E, Enulescu O, Caloinescu C. Catecholamine urinary excretion in cerebrovascular accidents. *Neurol Psychiatr (Bucur)* 1977;15:271–9.

Br Heart J 1987;57:490–1

Rupture of the sinus of Valsalva during pregnancy

T CRIPPS, C W PUMPHREY, D J PARKER

From the Regional Cardiothoracic Unit, St George's Hospital, London

SUMMARY A case is described in which rupture of the right sinus of Valsalva occurred at 37 weeks' gestation. The ruptured sinus was successfully repaired one week after the delivery of a healthy infant by caesarean section.

Rupture of a sinus of Valsalva has not been reported in pregnancy before. We describe such a case, and outline a successful management strategy.

Case report

A 22 year old Turkish Cypriot woman in week 37 of her first pregnancy attended her local hospital because of palpitation and chest pain. She had become aware of a sudden increase in her heart rate one week before when hanging out washing: there had been some retrosternal discomfort at the time. Subsequently a dry cough, dyspnoea, and orthopnoea had developed and a heart murmur was heard.

Examination showed tachypnoea on minor exertion. She had a sinus tachycardia of 110 beats/min. The carotid upstroke was sharp and the cardiac impulse was hyperdynamic. The jugular venous pressure was normal. On auscultation a continuous murmur was most strongly heard in mid-systole and at the left sternal edge. The blood pressure was 130/50 mm Hg in both arms. Examination was otherwise unremarkable for week 37 of pregnancy.

The chest radiograph showed increased vascular markings and the electrocardiogram was normal. The diagnosis was thought to be rupture of a sinus of Valsalva, though other causes of aortic run-off including aortic dissection with aortic valve regurgitation were considered. Caesarean section was performed and polyhydramnios was found. The patient was delivered of a healthy female infant. Echocardiography showed a probable defect in the right sinus of Valsalva (fig 1) but in view of the possibility of aortic dissection it was felt that angiographic confirmation of the diagnosis should be obtained. Aortography demonstrated the presence of a communication between the aorta and the right ventricle through the sinus of Valsalva (fig 2).

One week later the patient continued to have evidence of an important left to right shunt with a resting tachycardia and radiographic evidence of pulmonary venous congestion. Repair of the ruptured sinus was undertaken and an aneurysm was found. It arose from the right coronary sinus of Valsalva and communicated with the right ventricular outflow tract just below the pulmonary valve. The defect was repaired with sutures from both the aortic and right ventricular aspects.

Discussion

Since the first case of rupture of the sinus of Valsalva was described by Thurnam in 1840 over 200 cases

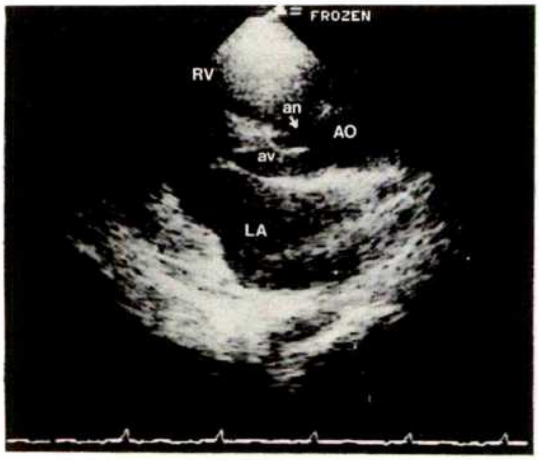

Fig 1 *Echocardiogram in long axis parasternal view showing a defect in the anterior aortic wall (an). Flow through the defect was demonstrated with pulsed wave Doppler. RV, right ventricle; LA, left atrium; AO, aorta; av, aortic valve.*

Requests for reprints to Dr T Cripps, Cardiac Department, St George's Hospital, Blackshaw Road, London SW17 0QT.

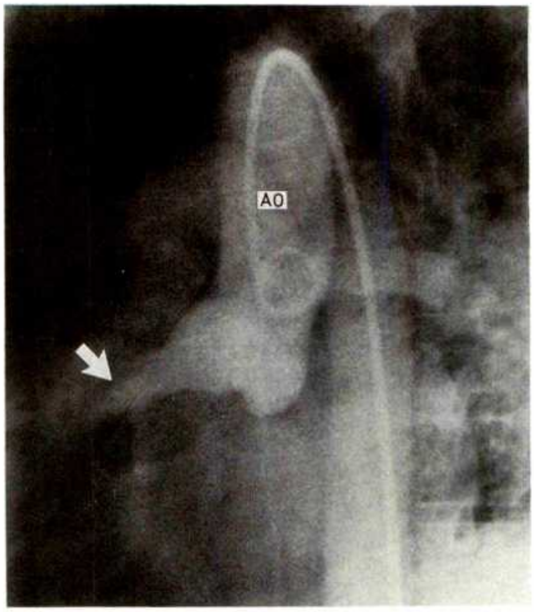

Fig 2 *Aortogram in the left anterior oblique projection showing regurgitation of contrast through a ruptured right sinus of Valsalva into the right ventricle. AO, aorta.*

have been reported[1] but this condition has not previously been described in pregnancy. Most cases of aneurysm of the sinus of Valsalva are thought to be congenital, probably resulting from a lack of continuity between the aortic media and the annulus fibrosis.[2] There may be an associated ventricular septal defect, coarctation of the aorta, or a bicuspid aortic valve. Other cases result from an inherited connective tissue abnormality, as in Marfan's syndrome or Ehlers-Danlos syndrome; from inflammatory disease, as in endocarditis, syphilitic or granulomatous aortitis, or Behçet's disease; and from mechanical disruption after stab wounds, aortic dissection, or after aortic valve replacement or ventricular septal defect repair. A congenital aneurysm may persist into middle age, when it may cause right ventricular outflow obstruction or may rupture into any of the four cardiac chambers, the pulmonary arteries, pericardium, or adjacent extravascular spaces. Echocardiography may allow the detection of the aneurysm before the onset of symptoms.[3]

This case was typical of the congenital type; perhaps rupture was precipitated by the hyperdynamic state of late pregnancy coupled with hormonally induced changes in the mechanical properties of connective tissue. It was felt that since the patient was already haemodynamically compromised, caesarean section was the preferred method of delivery. The risks of allowing vaginal delivery in this condition are unknown, since the condition has not been reported before in pregnancy, but it was thought likely that the haemodynamic changes occurring during labour would exacerbate the left to right shunt and perhaps extend the aneurysmal tear. After delivery, as would be expected, evidence of a continuing important left to right shunt was present, and the defect was corrected. A delay of several days was allowed, to minimise the risk of haemorrhage from the placental site. Although delivery can proceed without complications in heparinised patients, haemorrhage was still a risk. Ergometrine was contraindicated in the presence of a ruptured sinus of Valsalva.

In this case the optimal management was clear because the patient was close to term and so could be delivered without undue risk to the child. Had the patient presented earlier in pregnancy, the decision whether to allow pregnancy to continue would have depended on the balance between the risk to the child of an early delivery and the haemodynamic consequences to the mother of continuing to a later stage of pregnancy. In the event, she did not present until 37 weeks' gestation and the management described resulted in a successful outcome for both mother and child. This report parallels a recent one of acute aortic dissection during pregnancy,[4] and both illustrate a successful management strategy with prompt caesarean section and definitive early surgery for the maternal condition.

We are grateful to Mr M Pearce who conducted the obstetric management of this case.

References

1 Boutefeu JM, Moret PR, Hahn C, Hauf E. Aneurysms of the sinus of Valsalva. Report of seven cases and review of the literature. *Am J Med* 1978;**65**:18–24.

2 Edwards JE, Burchell HB. The pathological anatomy of deficiencies between the aortic root and the heart including aortic sinus aneurysms. *Thorax* 1957; **12**:125–39.

3 Desai AG, Sharma S, Kumar A, Hansoti RC, Kalke BR. Echocardiographic diagnosis of unruptured aneurysm of right sinus of Valsalva: an unusual cause of right ventricular outflow obstruction. *Am Heart J* 1985;**109**:363–4.

4 Pumphrey CW, Fay T, Weir I. Aortic dissection during pregnancy. *Br Heart J* 1986;**55**:106–8.

Br Heart J 1987;**57**:492–5

Correspondence

Incidence of spasm at the site of previous successful transluminal coronary angioplasty: effect of ergometrine maleate in consecutive patients

Sir,

Quyyumi *et al* (1986;**56**:27–32) report an increased sensitivity to ergometrine maleate (ergonovine maleate) at the site of previous successful transluminal coronary angioplasty in over a third of their patients. This finding has obvious clinical implications, especially with regard to restenosis. Unfortunately the illustrations of the coronary angiograms in fig 4 leave much to be desired. Fig 4b which is meant to show "successful dilatation of the stenosis" seems to show a rather severe narrowing in the proximal left anterior descending artery which does not appear to be much different from the original lesion shown in fig 4a and which was the very same site where spasm resulted from intravenous ergometrine shown in fig 4c. Thus I wonder if one is justified in calling the response an increased sensitivity if the coronary arterial lesion before ergometrine was already very tight. Although single frames from cineangiograms often do not do justice in depicting coronary lesions, I think the examples in fig 4 are certainly not very convincing. Authors generally tend to show their best products in their presentation; I wonder if Quyyumi *et al* have better examples than those published.

Tsung O Cheng,
Department of Medicine,
The George Washington University Medical Center,
The HB Burns Memorial Building,
2150 Pennsylvania Avenue, NW,
Washington, DC 20037,
USA.

This letter was shown to the authors, who reply as follows:

Sir,

We thank Dr Cheng for his comments. As Dr Cheng rightly points out, single frames from cineangiograms often do not do justice in depicting lesions. We have therefore reproduced in biplane views (figs 1 and 2) the pre-angioplasty and post-angioplasty lesion from the same patient as in our paper. We are sure that there can be little doubt that this patient did have a successful angioplasty.

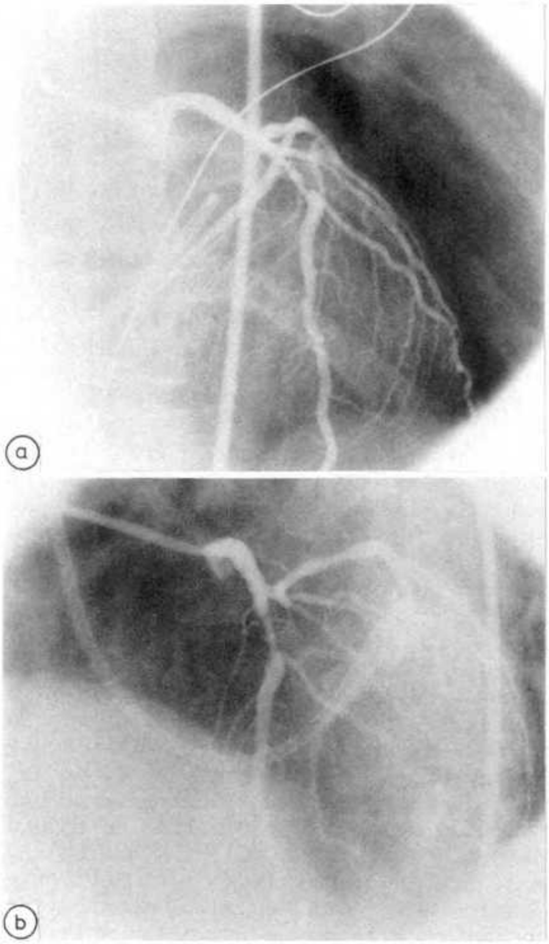

Fig 1 *Cineangiograms of the original lesion in proximal left anterior descending coronary artery. (a) Anteroposterior view; (b) left anterior oblique cranial view.*

LM Shapiro,
M Raphael,
A Rickards,
K Fox,
National Heart Hospital,
Westmoreland Street,
London W1M 8BA.

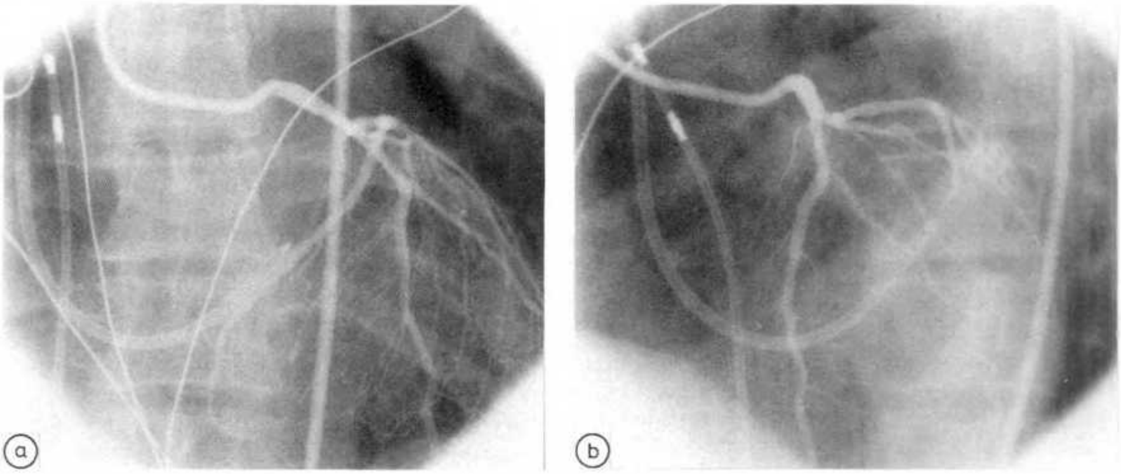

Fig 2 *Cineangiograms of similar views of the left anterior descending coronary artery demonstrating successful dilatation of the stenosis. (a) Anteroposterior view; (b) left anterior oblique cranial view.*

Early results after percutaneous transluminal coronary angioplasty in 400 patients

Sir,
Dr Sowton and coworkers (1986;**56**:115–20) report five angioplasty related deaths in the first 400 patients who underwent percutaneous transluminal coronary angioplasty at Guy's Hospital. In 1985, one of the authors of this study, Dr Timmis, presented the preliminary results to the Junior Cardiac Club. At that time, 254 patients had undergone the procedure and there had been six deaths. The mortality figures are recorded in the minutes of the Club, which are not published or distributed but are held by the President of the Club and available for inspection by members.

I should be grateful if the authors would explain whether changes in protocol or inclusion criteria account for these discrepancies in mortality figures.

Peter Wilmshurst,
Department of Cardiology,
St Thomas's Hospital,
London SE1 7EH.

This letter was shown to the authors, who reply as follows:

Sir,
The results in our paper were for the first angioplasty, as stated in our introduction. The presentation to the Junior Cardiac Club by Dr Timmis included results and complications in second or third angioplasties of patients who had recurrent angina. As also stated in our paper the results in patients who have relapse over a five year period will be presented in a separate communication.

Adam D Timmis,
Edgar Sowton,
Department of Cardiology,
Guy's Hospital,
St Thomas Street,
London SE1 9RT.

Diagnosis and prognosis of right ventricular infarction

Sir,
The important paper by Dr Rodrigues and colleagues (1986;56:19–26) showed that in a series of 51 patients with acute infarction of the inferior myocardial wall, right ventricular ejection fraction was depressed in all cases, while pyrophosphate scintigraphy was positive in 25 ($\simeq$50%) of the 51 patients. Moreover, severe right ventricular dysfunction was taken to be a right ventricular ejection fraction of $<0{\cdot}25$ and 50% of their patients fell into this category. They also argued that this stricter criterion (right ventricular ejection fraction $<0{\cdot}25$) enhances the specificity of radionuclide ventriculography in the diagnosis of right ventricular involvement.

We should like to make the following comments:

(*a*) It is surprising that they found a clear cut depression of right ventricular ejection fraction in all patients; this finding does not accord with the pathoanatomical[1] and radionuclide[2–4] reports and it suggests incorrect selection of the patient population. Did they exclude patients with chronic pulmonary obstructive disease, valvar heart disease, or right bundle branch block?

(*b*) Rodrigues *et al* obtained negative pyrophosphate scans in about half of their patients. If this finding is compared with that in (*a*), it follows that half of their patients showed right ventricular dysfunction in the absence of scintigraphic, and perhaps also clinical and electrocardiographic, findings consistent with right ventricular necrosis.

(*c*) Using a right ventricular ejection fraction $<0{\cdot}25$ as the criterion for right ventricular dysfunction Rodrigues *et al* reported involvement of the right ventricle in 50% of patients. What then, was the meaning of the lower limit (0·53) of normal range for right ventricular ejection fraction?

(*d*) Garty *et al* emphasised that regional wall motion abnormalities are the most constant finding with the greatest sensitivity and specificity in the diagnosis of right ventricular infarction.[4] We and our coworkers demonstrated a statistically significant correlation between depressed right ventricular ejection fraction and the presence of regional wall motion abnormalities of the right ventricle in a series of patients with acute infarction of the inferior myocardial wall.[5] Analysis of right ventricular regional wall motion was not reported by Rodrigues *et al*.

(*e*) Rodrigues *et al* did not report left ventricular ejection fractions in the acute phase of infarction (days 2 to 4) nor give details of treatment.

(*f*) Could Dr Rodrigues and colleagues explain why mean right ventricular ejection fraction was 0·21 in the 14 patients without clinical features of right ventricular dysfunction?

B Palagi,
R Picozzi,
R Baroffio,
Servizio di Medicina Nucleare and
Servizio di Cardiologia ed Unità Coronarica,
Ospedale di Saronno,
21047 Saronno (VA), Italy.

References

1 Wartman WB, Hellerstein HK. The incidence of heart disease in 2000 consecutive autopsies. *Ann Intern Med* 1948;28:41–65.
2 Sharpe DN, Botvinick EH, Shames DM, *et al*. The non-invasive diagnosis of right ventricular infarction. *Circulation* 1978;57:483–90.
3 Wackers FJ, Lie KI, Sokale EB, Res J, van der Schoot JB, Durrer D. Prevalence of right ventricular involvement in inferior wall myocardial infarction assessed with myocardial imaging with thallium-201 and technetium-99m pyrophosphate. *Am J Cardiol* 1978;42:358–62.
4 Garty I, Barzilay J, Bloch L, Antonelli D, Koltum B. The diagnosis and early complications of right ventricular infarction. *Eur J Nucl Med* 1984;9:453–60.
5 Palagi B, Baroffio R, Picozzi R, *et al*. Radionuclide assessment of right ventricular involvement in inferior acute myocardial infarction.clinical correlations and in-hospital follow-up *Eur J Nucl Med* 1985; 10:235–40.

This letter was shown to the authors who reply as follows:

Sir,

We thank Dr Palagi and colleagues for their interest in our paper and for their comments. They pose a number of questions which we will try to answer succinctly.

Patient selection is important; our patients had been admitted to our coronary care unit and over 90% had sustained transmural myocardial infarction. We excluded patients with chronic obstructive pulmonary disease or valvar heart disease. We have previously reported that after anterior transmural anterior myocardial infarction left ventricular ejection fraction was below the lower limit of normal in virtually all patients and was $<0·25$ in 40%.[1] In that study gross right ventricular dysfunction as detected empirically by right ventricular enlargement and abnormal wall movement was seen in 43% of all patients surviving inferior infarction.

Dr Palagi and colleagues may have misunderstood the point regarding pyrophosphate scintigraphy. All patients had a positive uptake in the myocardium, but only in 25 was the uptake detectable in the right ventricle. We discussed the possible reasons for negative pyrophosphate scintigrams in the text.

The aim of our study was to compare the reliability of the various non-invasive diagnostic methods of determining the frequency of right ventricular involvement in acute inferior wall myocardial infarction and, more importantly, to examine the clinical implications and prognosis of right ventricular involvement. By using the arbitrary figure of 0·25 for right ventricular ejection fraction we were able to identify those patients with more severe right ventricular dysfunction whose clinical progress was likely to be complicated both in the short and the long term. Those with less pronounced right ventricular dysfunction (ejection fraction 0·25 to 0·53) showed subsequent improvement in right ventricular function and in the main their progress has been satisfactory. The results would not have been substantially different if the equally arbitrary value of 0·3 for right ventricular ejection fraction had been taken.

Wall motion analysis was performed with phase analysis and, as stated in the summary, persisting right ventricular dyskinesia was evident in six patients with poor residual ventricular function, but when a segmental wall motion score was used as an isolated variable it was not of further discriminant value. The complex anatomy of the right ventricle, however, makes the accurate study of abnormal wall motion difficult from any assessment in a single plane.

Our report showed left ventricular ejection fraction at days 2 to 4 which is at a comparable time to our previous study[1] and after the spontaneous acute changes in left ventricular ejection fraction in the first 24 hours have subsided. Treatment was standardised according to our own therapeutic schedule and there were no deviations from this.

Finally, we suggest that right ventricular infarction only becomes clinically apparent when gross right ventricular damage is sustained. Should accurate non-invasive methods of diagnosis be unavailable we believe that the index of clinical suspicion for right ventricular dysfunction should be high in all cases of transmural inferior myocardial infarction. We have reread the paper by Dr Palagi and colleagues and we suggest that our paper supports their final conclusion "that the characteristic feature of inferior MI is a decreased RVEF . . .".[2] Different patient selection is the likeliest reason for the variation in the reported frequency of poor right ventricular function.

AL Muir,
NG Dewhurst,
Department of Medicine,
The Royal Infirmary,
Edinburgh EH3 9YW.

EA Rodrigues,
Cardiology Department,
Northwick Park Hospital and Clinical Research Centre,
Watford Road,
Harrow, Middlesex HA1 3UJ.

References

1 Dewhurst NG, Muir AL. Comparative prognostic value of radionuclide ventriculography at rest and during exercise in 100 patients after first myocardial infarction. *Br Heart J* 1983;**49**:111–21.

2 Palagi B, Baroffio R, Picozzi R, *et al*. Radionuclide assessment of right ventricular involvement in inferior acute myocardial infarction: clinical correlations and in-hospital follow-up. *Eur J Nucl Med* 1985;**10**:235–40.

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Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

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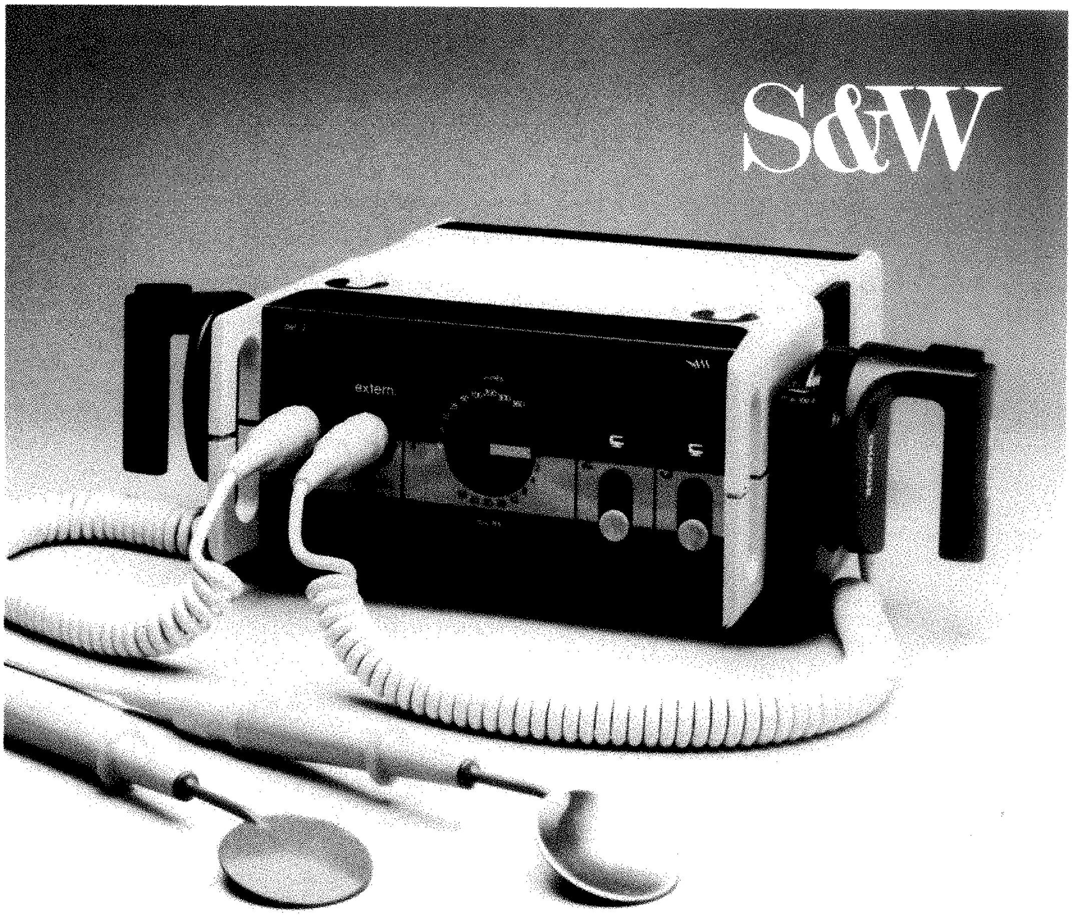

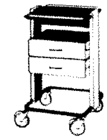
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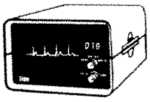
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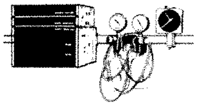
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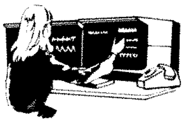
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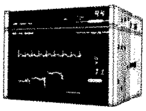
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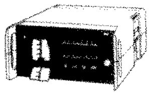
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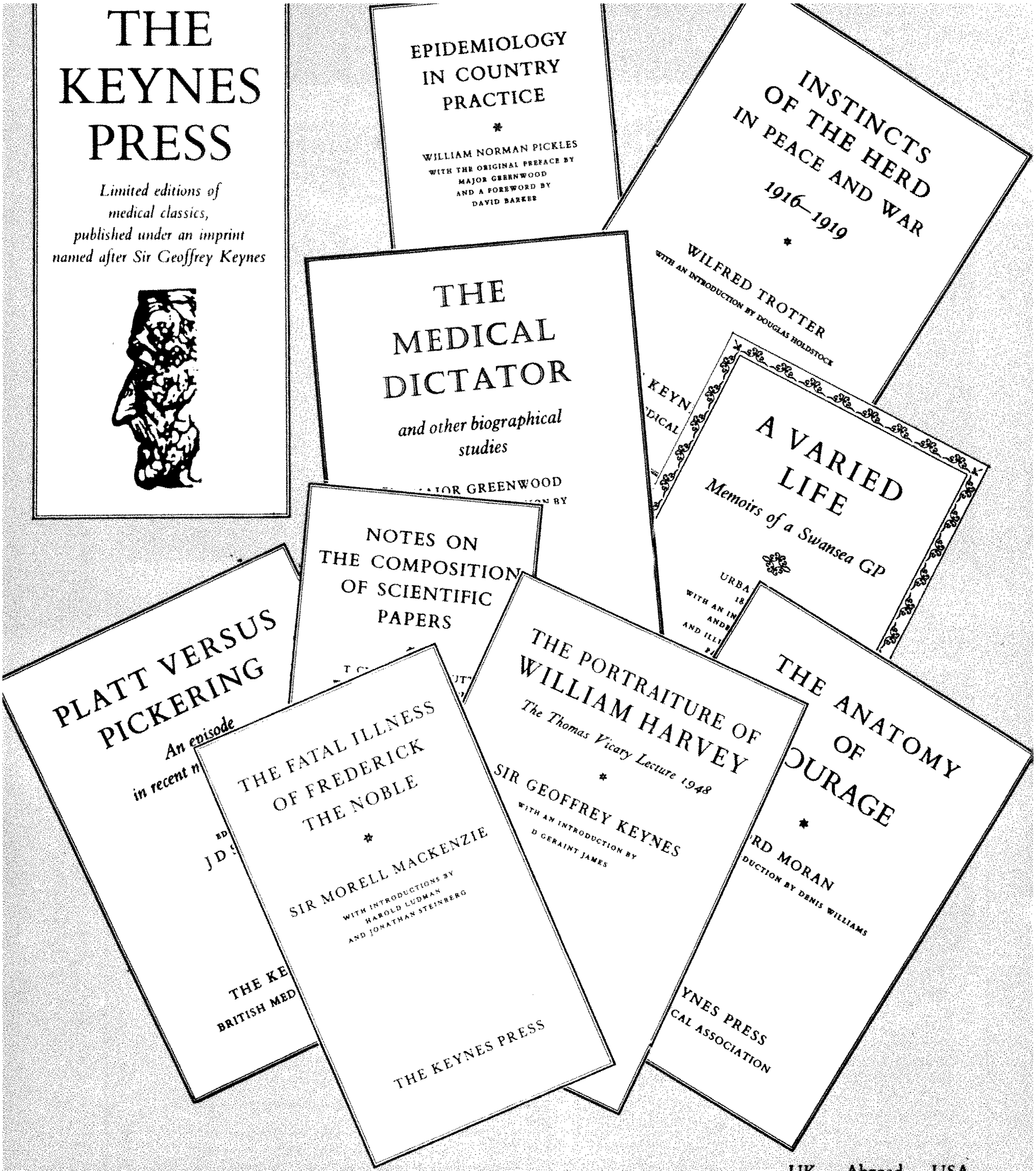
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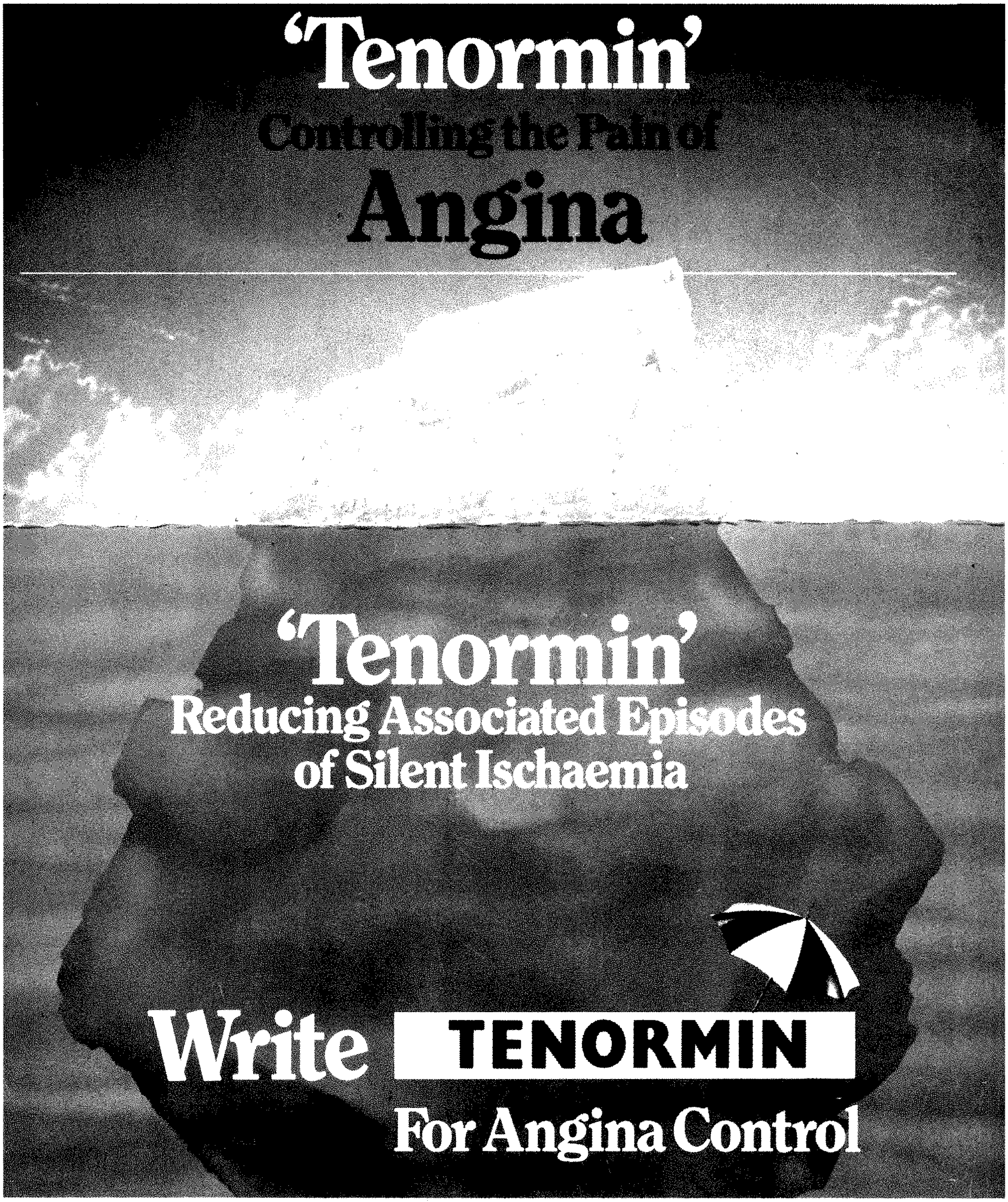

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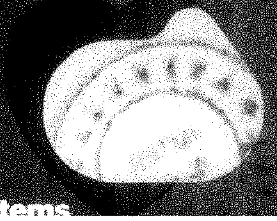

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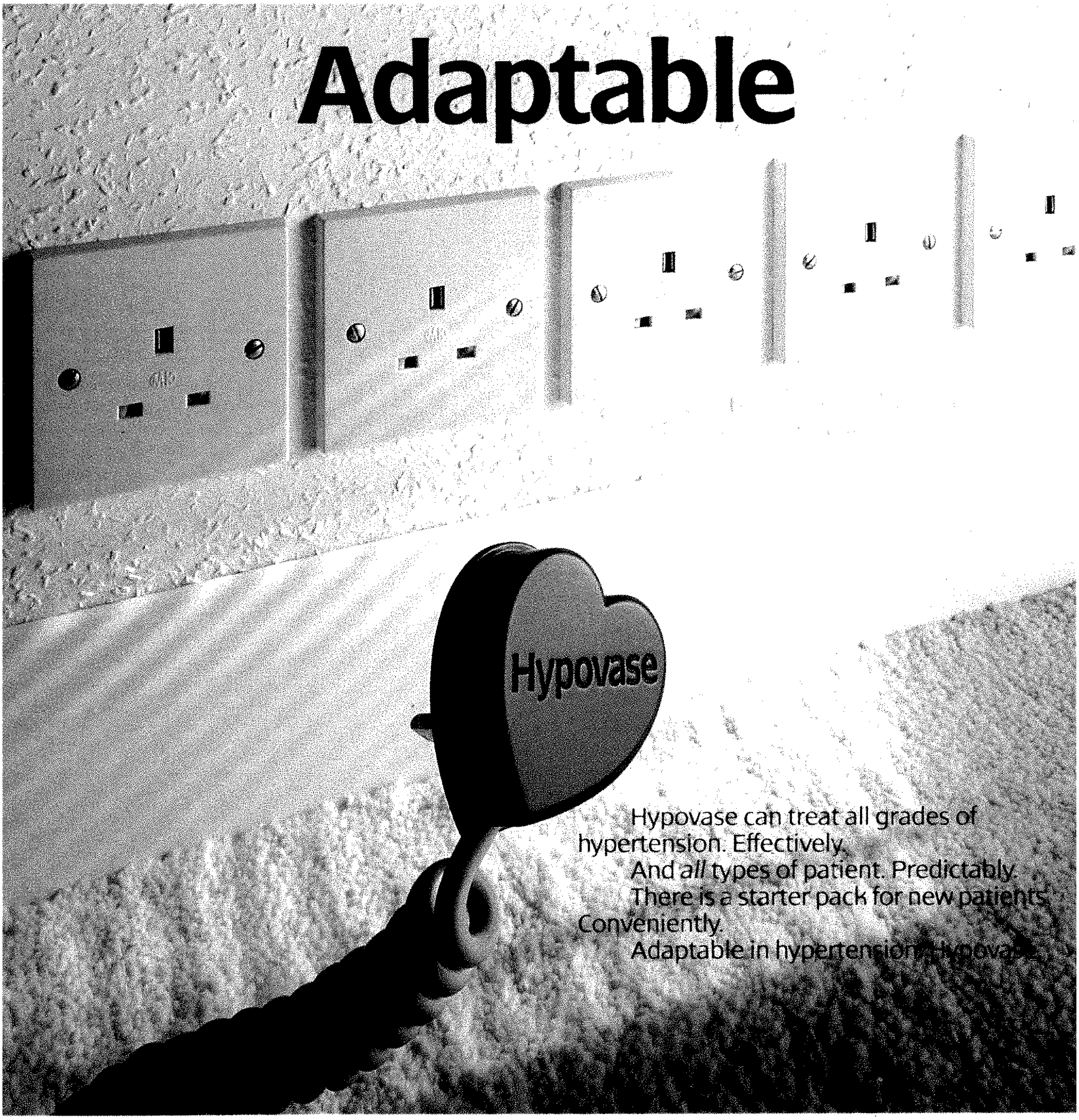

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D G JULIAN

From the British Heart Foundation, London

Coronary heart disease excited little interest among cardiologists in the 1950s. In 1959 only six out of 65 articles in the *British Heart Journal* were on coronary disease and in 1964 seven of 89 articles were on ischaemic heart disease and 28 on congenital heart disease. There were, however, those who were concerned about how little we then knew about myocardial infarction, among them Professor (now Sir John) McMichael, who initiated research in this field at Hammersmith Hospital, and Gunnar Biorck of Stockholm who wrote: "There are few diseases in the sphere of internal medicine where the average mortality during four to six weeks hospitalization is over 30%, and if the patients with shock are particularly considered, the figure is more than twice as large. It is obvious that the task of treatment and prevention is tremendous and it appears necessary that more energy be directed to a considerable reduction in these figures. The mere quantity of the problem may have prevented us from calling all forces to arms in the 'infarct battle'. However, our surgical colleagues would never accept a mortality of this magnitude and would certainly mobilize personnel and technique to bring such figures down."[1]

In fact, important advances had been taking place, although their relevance to patients with acute coronary heart attacks were not initially appreciated. Beck and colleagues in 1947 had resuscitated, by electric shock, a 14 year old boy in whom ventricular fibrillation developed during operation[2]; nine years later, Beck's group was successful in correcting ventricular fibrillation, using open thoracotomy, in a 65 year old physician with a myocardial infarction.[3] This led them to write, with remarkable foresight, "This one experience indicates that resuscitation from a fatal heart attack is not impossible and might be applied to those who die in the hospital and perhaps to those who die outside the hospital."[3] They concluded "The veil of mystery is being lifted from heart conditions, and the dead are being brought back to life." Many surgeons then became trained in the techniques of open chest cardiac massage, but cardiac resuscitation was not taught or discussed by physicians. In the next five years about 20 cases of resuscitation after myocardial infarction were reported.

These reports of the successful treatment of "sudden death" stimulated interest at the Royal Infirmary, Edinburgh, and we decided to treat cardiac arrest complicating myocardial infarction by thoracotomy, open chest massage, and defibrillation if the circumstances were propitious. On 5 May 1960, a 40 year old physician with a myocardial infarction collapsed on admission to the ward. A scalpel, which was poised to incise a cubital fossa in an adjacent catheterisation laboratory, was diverted to initiate a thoractomy. After some minutes, help became available from our surgical colleagues, who performed more effective cardiac massage until internal defibrillation could be carried out. The patient made an excellent cardiac recovery (he sustained some cerebral damage but survived for 23 years). By a curious quirk of fate he was an alumnus of Johns Hopkins Hospital, and shortly after his recovery he showed us an article in the hospital journal describing closed chest cardiopulmonary resuscitation, which had been developed there by Kouwenhoven, Jude, and Knickerbocker [4] We had by this time resuscitated (temporarily) two other patients by open chest techniques, and we used closed chest massage for a further two patients in that year. Although they both died later, it was apparent that our inability to keep more than one of our five patients alive was due to the delay in initiating treatment and lack of skills in the staff at hand. It, therefore, seemed appropriate to write:

Requests for reprints to Professor D G Julian, British Heart Foundation, 102 Gloucester Place, London W1H 4DH

"Many cases of cardiac arrest associated with acute myocardial ischaemia could be treated successfully if all medical, nursing, and auxiliary staff were trained in closed-chest cardiac massage and if the cardiac rhythm of patients with acute myocardial infarction were monitored by an electrocardiogram linked to an alarm system." ... "All wards admitting patients with acute myocardial infarction should have a system capable of sounding an alarm at the onset of an important rhythm change and of recording the rhythm automatically on an ECG." ... "The provision of the appropriate apparatus would not be prohibitively expensive if these patients were admitted to special intensive-care units. Such units should be staffed by suitably experienced people throughout the 24 hours."[5]

This first description of what later became known as the coronary care unit was presented to the British Thoracic Society in July 1961, and published in the *Lancet* shortly afterwards.[5] When these concepts were proposed to the medical staff of Sydney Hospital (notably Dr Malcolm Whyte and Dr Gaston Bauer) they were welcomed enthusiastically and plans were put in hand in October 1961 to provide the necessary beds, apparatus, and staff training. Monitoring of patients with myocardial infarction started early in 1962 and became routine in Sydney Hospital later in that year. Virtually simultaneously, Day in Kansas, Meltzer in Philadelphia, and Brown in Toronto started similar units. In 1963, units were opened in Melbourne by Sloman, in New York by Grace, and in Miami by Ungar, but few others started in the next year. The picture changed dramatically, particularly in North America, after the publication of the first reports by Day[6] and Brown *et al.*[7] The first report from Sydney was rejected by the *Lancet*, because the journal had recently accepted Brown *et al*'s article, and by the *British Medical Journal* because "it was irresponsible to suggest that all patients with acute myocardial infarction should be admitted to wards in which they can receive intensive care." It was published nine months later in the *Medical Journal of Australia.*[8]

The first presentation of coronary care given to the British Cardiac Society was at the Autumn meeting in 1964 when the Sydney experience was described. At the same meeting Shillingford and his colleagues reported the setting up of a special unit at Hammersmith Hospital for the intensive investigation of myocardial infarction.

Meltzer and Kitchell, in a historical review of coronary care units, described five phases in their development: the resuscitation phase, the phase of vigorous management of arrhythmias, the phase of the vigorous investigation and treatment of pump failure, the phase of out of hospital coronary care, and a final phase aimed at the prevention of sudden death.[9] To this, Norris has added a sixth phase—that of trials for restriction of infarct size.[10]

The phase of resuscitation

It was essentially the successes of closed chest cardiac resuscitation that triggered the creation of what Day christened the coronary care unit. Initial results of treating ventricular fibrillation were not good, but rapidly improved as more staff were trained. Thus in Sydney only one of the first nine patients survived compared with six of the next 15.[11] A crucial advance, not only in coronary care but in hospital medicine generally, was giving nurses the responsibility for the detection and treatment of arrhythmias (including defibrillation). Meltzer and Kitchell in Philadelphia, who were responsible for this development, writing about their early experience said "Informal attempts were made to monitor selected patients (using makeshift equipment) by having a rotating team of house offcers remain in constant attendance in the unit. The results were dismal: the resident physicians were hopelessly bored with the inactivity and the seemingly endless vigil, and it became necessary to discontinue the effort abruptly to avoid (what now would be called) a demonstration. By default, a system of specialized care was then conceived wherein nurses rather than physicians assumed the primary responsibility for surveillance as well as for emergency treatment."[9]

By the late 1960s all units were reporting excellent results in cases of primary ventricular fibrillation but a low success rate in those in whom this arrhythmia had been preceded by shock or cardiac failure. In the 20 years since then the situation has remained much the same.

The attack on arrhythmias

Curiously, although the first four coronary care units used similar methods of monitoring they came to rather different conclusions about the major mechanism of death. Day found that asystole was the commonest arrhythmic problem (eight of 11 cardiac arrests)[6] and Brown *et al* reported that ventricular fibrillation was relatively uncommon[7]; whereas in Philadelphia[12] and Sydney[11] ventricular fibrillation was considered to be the greatest single cause of death. These differences probably reflected the different types of patient admitted to the four units. Eventually, the results of these and other units proved similar, with ventricular fibrillation being seen in 8–10% of patients.

Workers in the earliest coronary care units had all been intensely interested in arrhythmias and conduction disorders and it had soon become apparent that arrhythmias were much more common than had previously been suspected.[11] Particular attention was paid to ventricular extrasystoles because they were found to be almost universal. This interest culminated in the classic paper by Lown's group which reported that not one of 300 patients with myocardial infarction developed ventricular fibrillation.[13] They attributed this remarkable result to the detection of "warning" arrhythmias and their treatment with lignocaine.

After this report there was a tremendous enthusiasm for the detection of arrhythmias and in many units nurses were instructed to intervene at the first sign of "ectopy". Increasingly they were expected to identify even the most rare arrhythmias and to become experts in fascicular blocks. Not surprisingly, scepticism eventually crept in, with Lie *et al*[14] in Amsterdam and El-Sherif and his colleagues[15] in Miami actually having the temerity to doubt the existence of "warning arrhythmias". It has now become fairly clear that there is a relation, albeit rather weak, between the R-on-T phenomenon and primary ventricular fibrillation, but the other ventricular arrhythmias including ventricular tachycardia are about as common in those who do not develop primary ventricular fibrillation as in those who do.[16] The relation between warning arrhythmias and secondary ventricular fibrillation has never been satisfactorily studied.

The development of coronary care coincided with a rapid expansion in the use of transvenous pacing. As with ventricular arrhythmias, indications for treatment were progressively widened so that in 1967 transvenous pacing electrodes were inserted in 35% of patients with myocardial infarctions in the New York Hospital–Cornell Medical Center.[9] Subsequently, the relatively benign course of sinus bradycardia and of heart block in inferior myocardial infarction became clearer and electrodes are now much less frequently used than they were.

The attack on pump failure

With the successes in resuscitation and the ability to control arrhythmias and conduction disorders the main causes of death became advanced left ventricular failure and cardiogenic shock. Before the introduction of coronary care units there had been few studies of the cardiorespiratory consequences of myocardial infarction, partly perhaps because of the expected risks of invasive investigation. By the time of the first international meeting on coronary care, held in Edinburgh in 1967,[17] a large amount of information had been gathered, notably by Malmcrona and Varnauskas in Sweden,[18] by Shillingford's group at Hammersmith,[19] by Mackenzie[20] in Donald's group in Edinburgh, and by Nixon at Charing Cross Hospital.[21] Shortly afterwards the Myocardial Infarction Research Units (MIRU) were created in the United States and a large programme of research was initiated into the investigation of the haemodynamic effects of myocardial infarction. It had been shown that the commonly used right atrial and "central venous" pressures provided an unreliable index of left sided function[22]; the introduction of the Swan-Ganz[23] flow guided catheter was a major advance in the evaluation of cardiac performance in the coronary care unit. This allowed the more precise delineation of the various haemodynamic subsets of patients[24] with myocardial infarction and facilitated their more rational treatment.

Enthusiasm for invasive monitoring has varied enormously from one centre to another. In many hospitals, notably in the United States and Australia, invasive monitoring became virtually routine while in the United Kingdom only a few hospitals have had the facilities and expertise to use it. At present it is probably true to say that it is used in a small proportion of cases (perhaps 5–15%) even in those institutions that have access to invasive monitoring. Its use is largely dictated by clinical indications. These are essentially cardiogenic shock and severe left ventricular failure, and few would question the advisability of having precise measurements of left and right-sided pressures when potent inotropic and vasodilator drugs are being used. The cost of the resources and drugs used in complicated myocardial infarction is considerable and it is unfortunate that we still have no well controlled studies of the value of such investigations and the effect of such treatments.

Prehospital coronary care

The introduction by Pantridge and his colleagues of prehospital coronary care in 1966 was an advance of the greatest importance.[25] Prehospital care was also developed in the Soviet Union but the concepts were quite different from those of Pantridge—the primary concern was with the treatment of cardiac failure and shock rather than the prevention and treatment of cardiac arrest. In 1968 Chazov wrote: "Fibrinolytic therapy (streptokinase) is started within the first hours after the onset of the disease. The treatment is derived from the fact that thrombosis of the coronary arteries is revealed in 70–80% of myocardial infarction cases. When started early and carried out for a sufficiently long time ... this therapy leads to marked improvement in the course of myocardial infarction—rapid control of pain, less cardiac failure, less rise of blood transaminase, and more rapid signs of ECG healing. The effect of the therapy is associated with the action of the preparations on the principal thrombus, but also with the spasmolytic properties of heparin and fibrinolytic enzymes. In addition, the effect on the so-called secondary thrombi is of great significance in reducing the area of ischaemia and necrosis."[26]

Because Geddes recently reviewed the 20 year history of prehospital coronary care[27] I will not consider this aspect further. It has taken all of these 20 years to achieve acceptance, at least in the United Kingdom, but at last it seems that there is general enthusiasm for prehospital coronary care and the Department of Health and Social Security is encouraging the extended training of ambulancemen. Paradoxically, whereas the realisation that techniques of coronary care can be practised by paramedical personnel finally led to this change of approach, a reversion to Pantridge's original approach of using doctors for prehospital care will probably follow the introduction of thrombolytic treatment.

Limitation of infarct size

The idea that early intervention might limit the eventual extent of infarction was implicit in Pantridge's development of the mobile coronary care unit[28] and made explicit by Chazov,[26] but the concept of limitation of infarct size also owes much to the work of Maroko and Braunwald.[29] More than 30 forms of treatment have been tried out in animals or man with this aim in view; so far only β blockers[30 31] and thrombolytic agents[32 33] appear to have stood the tests of time and clinical trials. Convincing evidence of the value of these treatments has only been forthcoming recently and it is too soon to know how widely they will be used and what their impact will be on coronary care. Thrombolytic treatment must be started as early as possible; however, admission of coronary patients to intensive care is still deplorably slow. In the late 1960s and early 1970s the median time from the onset of symptoms to admission to coronary care units was usually 5–6 hours; it is probably no better now except where prehospital schemes are in force. Indeed, there are teaching hospitals where the median admission times are in excess of eight hours. It is clear that there must be major initiatives inside and outside hospital to accelerate the care of patients with acute myocardial infarction.

The effectiveness of coronary care units

If the British were rather slow in implementing coronary care, they were not backward in questioning its value. Cochrane in 1972 wrote that "the battle for coronary care is just beginning."[34] Rose was particularly critical of the early units for not more carefully comparing their experiences before and after the introduction of coronary care and he also suggested that if intensive coronary care were indeed effective there should have been some impact on national mortality figures.[35]

In fact, in Edinburgh an administrator with a special expertise in epidemiology was asked to advise on the assessment of the effect of the opening of the unit, and a research fellow was appointed to undertake this. During the first year of operation of the unit mortality was 16·4%, compared with 23·4% in an apparently comparable group of cases in the preceding year.[36] Ninety one (15%) of the first 600 patients died; however, a further 25 (4%) of the patients became long term survivors of ventricular fibrillation. The mortality had, therefore, been reduced by 21% by this means alone. Others who compared mortality in the general wards with that of the coronary care unit included Meltzer,[37] Hofvendahl,[38] and Brown and MacMillan[39]; all reported a substantially lower mortality in the coronary care unit.

Another approach to the assessment of the potential of coronary care was the setting up of the Edinburgh Community Study,[40] which sought to determine the number of heart attacks in the community and their management. It became apparent that even such a study could not accurately assess the impact of coronary care on the community, although it confirmed the high incidence of early deaths that could not be affected by conventional coronary care. A clear cut immediate effect on the number of coronary deaths in Edinburgh was not expected because these had been increasing in the preceding years. In the United States, Australia, and New Zealand, however, where the institution of coronary care has been most extensively promoted, the mortality of those between the ages of 35–64 has been falling since 1967[41] (the time of the widespread introduction of coronary care units). It is clearly wrong to attribute most of the fall in mortality rates in the countries cited to the introduction of coronary care units; Reader suggested that it might be responsible for at least 20% of this reduction.

All these attempts to assess the effectiveness of coronary care units were unquestionably of dubious validity. In 1967 Oliver and his colleagues, who already had had extensive experience of clinical trials, pointed out why it would be virtually impossible to carry out a valid randomised control trial of coronary care units.[42] None the less, trials of home versus hospital treatment were mounted in Bristol and south west England,[43] and in Nottingham.[44] Essentially, both studies found that there was little or no benefit from hospital treatment. These results have been extensively debated since and this is not the place to repeat the arguments. In any case, our knowledge of how to conduct clinical trials has increased enormously since then. In particular, we have learned of the importance of ensuring that the study has sufficient power before concluding that a treatment is ineffective. Furthermore, we must be sure that the treatment (whether we are using drugs, surgical treatment, or resuscitation techniques) is being competently applied to those most likely to benefit from it before we damn it. Despite their defects, these studies did serve a very important function in drawing attention to the fact that intensive care can have no significant impact on mortality in low risk groups (such as those in good condition several hours after the onset of symptoms).

The future of coronary care units

CORONARY CARE OR CARDIAC CARE?

Many of the patients admitted to coronary care units have not sustained a myocardial infarction. The units have been of inestimable value in treating patients with arrhythmias and in managing unstable angina and other cardiac emergencies. "Coronary care unit" is therefore a widely accepted misnomer; "cardiac care unit" is perhaps a more accurate term but it does not seem to have the same appeal.

SHOULD CORONARY CARE BE PART OF INTENSIVE CARE?

At one time there was the widespread feeling that coronary care units should be integrated with intensive care units. This has not happened to any great extent, although there are some successful examples. Combined units can work well provided that the cardiac beds form a distinct part and a cardiologist is responsible for the cardiological training and practices of the staff.

SHOULD CORONARY CARE UNITS BE LINKED TO CARDIAC CATHETERISATION AND CARDIAC SURGICAL FACILITIES?

The role of cardiac catheterisation, angioplasty, and cardiac surgery is increasing in the management of patients admitted to coronary care units for myocardial infarction, unstable angina, or arrhythmias. The various facilities in cardiac centres must be designed to take account of these functions.

HOW CAN THE BENEFITS OF CORONARY CARE BE MAXIMISED AND ITS COSTS MINIMISED?

Coronary care remains an expensive form of management that can only be justified if it is restricted to those patients likely to benefit from it. The most urgent need is to accelerate the initiation of coronary care, including the administration of thrombolytic treatment, outside and inside hospital. Cardiologists throughout the United Kingdom should attempt to ensure that prehospital coronary care is improved, and that the physicians in the 25% of hospitals that do not have cardiologists are made aware of the importance of implementing appropriate acute coronary management.

Simpler and cheaper methods need to be devised to monitor patients whose only major risk is ventricular fibrillation, and the effectiveness of expensive invasive monitoring and the newer forms of treatment of shock and cardiac failure needs to be evaluated in controlled trials.

References

1 Biorck G. Fundamental problems in coronary heart disease. *Acta Med Scand* 1960;**168**:245–50.

2 Beck CF, Pritchard WH, Feil HS Ventricular fibrillation of long duration abolished by electric shock. *JAMA* 1947;**135**:985–6.

3 Beck CF, Weckesser EC, Barry FM. Fatal heart attack and successful defibrillation: new concepts in coronary artery disease. *JAMA* 1956;**161**:434–6.

4 Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed-chest cardiac message. *JAMA* 1960;**173**:1064–7.

5 Julian DG Treatment of cardiac arrest in acute myocardial ischaemia and infarction. *Lancet* 1961;**ii**:840–4.

6 Day HW An intensive coronary care area. *Dis Chest* 1963;**44**:423–7.

7 Brown KWG, MacMillan RL, Forbath N, Mel'Grano, F, Scott JW. Coronary unit. An intensive care centre for acute myocardial infarction. *Lancet* 1963;**ii**:349–52.

8 Julian DG, Valentine PA, Miller GG. Routine electrocardiographic monitoring in acute myocardial infarction. *Med J Aust* 1964;**i**:433–6.

9 Meltzer LM, Kitchell JB. The development and current status of coronary care. In: Meltzer LM, Dunning AJ, eds. *Textbook of coronary care* Amsterdam: Excerpta Medica, 1972:3–25.

10 Norris RM. *Myocardial infarction.* Edinburgh: Churchill Livingstone, 1982 143.

11 Julian DG, Valentine PA, Miller GG. Disturbances of rate, rhythm and conduction in acute myocardial infarction *Am J Med* 1964;**37**:915–27.

12 Meltzer LM, Kitchell JB. The incidence of arrhythmias associated with myocardial infarction. *Prog Cardiovasc Dis* 1966;**9**:50–63.

13 Lown B, Fakhro AM, Hood WB, Thorn GW. The

coronary care unit, new perspectives and directions. *JAMA* 1967;**199**:188–98.

14 Lie KI, Wellens HJJ, Downar E, Durrer D. Observations on patients with primary ventricular fibrillation complicating acute myocardial infarction. *Circulation* 1975;**52**:75–9.

15 El-Sherif N, Myerburg RJ, Scherlag BJ, *et al.* Electrocardiographic antecedents of primary ventricular fibrillation. Value of the R-on-T phenomenon in myocardial infarction. *Br Heart J* 1976;**38**:415–22.

16 Campbell RWF, Murray A, Julian DG. Ventricular arrhythmias in first 12 hours of acute myocardial infarction. Natural history study. *Br Heart J* 1981;**46**:351–7.

17 Julian DG, Oliver MF, eds. *Acute myocardial infarction.* Edinburgh: Livingstone, 1968.

18 Malmcrona R, Varnauskas E. Haemodynamics in acute myocardial infarction. *Acta Med Scand* 1964;**175**: 1–8.

19 Thomas M, Malmcrona R, Shillingford JP Hemodynamic changes in patients with acute myocardial infarction. *Circulation* 1965;**31**:811–8.

20 Mackenzie GJ, Taylor SH, Flenley DC, McDonald AH, Staunton HP, Donald KW. Circulatory and respiratory studies in myocardial infarction and cardiogenic shock. *Lancet* 1964;**ii**:825–8.

21 Nixon P. Observations in cardiogenic shock. In: Julian DG, Oliver MF, eds. *Acute myocardial infarction.* Edinburgh: Livingstone, 1968:191–5.

22 Rapaport E, Scheinman M. Rationale and limitations of hemodynamic measurements in patients with acute myocardial infarction *Mod Concepts Cardiovasc Dis* 1969;**38**:55–60.

23 Swan HJC, Ganz W, Forrester JS, Marcus H, Diamond G, Chonette D. Cardiac catheterization with a flow-directed balloon-tipped catheter. *N Engl J Med* 1970;**283**:447–51.

24 Forrester JS, Diamond G, Chatterjee K, *et al* Medical therapy of acute myocardial infarction by the application of hemodynamic subsets. *N Engl J Med* 1976;**295**:1356–62.

25 Pantridge JF, Geddes JS. A mobile coronary care unit in the management of myocardial infarction. *Lancet* 1967;**ii**:271–3.

26 Chazov EI. First aid in myocardial infarction. In: Julian DG, Oliver MF, eds *Acute myocardial infarction.* Edinburgh: Livingstone, 1968:313–6.

27 Geddes JS. Twenty years of prehospital coronary care. *Br Heart J* 1986;**56**:491–5.

28 Pantridge JF. The effect of early therapy on the hospital mortality from acute myocardial infarction [Abstract] *Q J Med* 1970;**39**:621–2.

29 Maroko PR, Kjekshus JK, Sobel BE, *et al.* Factors influencing infarct size following experimental coronary artery occlusion. *Circulation* 1971;**43**:67–83.

30 MIAMI Trial Research Group. Metoprolol in acute myocardial infarction. *Eur Heart J* 1985;**6**:199–226.

31 ISIS-1 Collaborative Group. A randomized trial of 16207 cases of acute myocardial infarction. *Lancet* 1976;**ii** 57–66.

32 Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI). Effectiveness of thrombolytic therapy. *Lancet* 1986;**i**:397–402.

33 ISIS Steering Committee. Intravenous streptokinase given within 0–4 hours of onset of myocardial infarction reduced mortality in ISIS-2 *Lancet* 1987;**i**:502.

34 Cochrane AL. *Effectiveness and efficiency.* London: Nuffield Hospital Trust, 1972.

35 Rose G. The contribution of intensive coronary care. *Br J Prev Soc Med* 1975;**29**:147–50.

36 Julian DG. Coronary care and the community. *Ann Intern Med* 1968;**69**:607–13.

37 Meltzer LE. Presbyterian-University of Pennsylvania Medical Center, Philadelphia. In. Julian DG, Oliver MF, eds. *Acute myocardial infarction.* Edinburgh: Livingstone, 1968:3–6.

38 Hofvendahl S. Influence of treatment in a coronary care unit on prognosis in acute myocardial infarction. *Acta Med Scand* 1971;suppl 519:1–78.

39 Brown KWG, MacMillan RL. The effectiveness of the system of coronary care. In: Meltzer LE, Dunning AJ, eds. *Textbook of coronary care.* Amsterdam: Excerpta Medica, 1972:52–7.

40 Armstrong A, Duncan B, Oliver MF, *et al.* Natural history of acute coronary heart attacks. A community study. *Br Heart J* 1972;**34**:67–80

41 Reader R. Why the decreasing mortality from coronary heart disease in Australia? *Circulation* 1978;**58** (suppl II):32.

42 Oliver MF, Julian DG, Donald KW. Problems in evaluating coronary care units *Am J Cardiol* 1967;**20**:465–74.

43 Mather HG, Morgan DC, Pearson NG, *et al.* Myocardial infarction: a comparison between home and hospital care for patients. *Br Med J* 1976;**i**:925–9.

44 Hill JD, Hampton JR, Mitchell JRA. A randomised trial of home versus hospital management for patients with suspected myocardial infarction. *Lancet* 1978;**i**:837–41.

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Editorial

Heart rate/ST slope

RAPHAEL BALCON

From the London Chest Hospital, London

In 1979 Berenyi *et al* first proposed that the rate of change of ST segment with respect to heart rate (the HR/ST slope) might be an indicator of the amount of prejudiced myocardium as judged by the coronary arteriogram.[1] This suggestion has been extensively studied particularly by the Department of Cardiovascular Studies at The University of Leeds. In 1982 these workers reported an excellent correlation between the slope and the number of main vessels with at least 75% stenosis, with no overlap of the slope ranges for one, two, and three vessel disease.[2]

Because heart rate is an important determinant of myocardial oxygen consumption it seems logical to propose that a relation between the degree of ischaemia and the heart rate could be used to assess the severity of coronary disease. A direct relation between the maximum ST depression in a single electrocardiographic lead and the degree of ischaemia is more difficult to accept since it assumes that all areas of the left ventricular myocardium are equally "accessible" to one of the 13 leads monitored and that the same amount of ischaemic myocardium anywhere in the heart will produce the same ST depression.

The arterial supply to the left ventricle is variable and equivalent stenoses in two arteries do not necessarily produce the same amount of ischaemic myocardium. The most obvious example of this is the extreme variability in the size and number of branches of the right coronary artery. Coronary calibre also varies from time to time and it would be surprising if there was a given level of critical stenosis (such as 75%). There are important additional problems posed by the known inaccuracies of visual interpretation of angiograms.

Nevertheless, had the findings been reproducible the test would have been extremely valuable for determining which patients should be referred for angiography. Other workers, however, have not been able to reproduce the results. Some found no correlation at all[3 4] and Okin *et al* reported a limited relation that identified patients with triple vessel disease.[5]

Kligfield *et al* recently summarised their own data and reviewed the arguments. They concluded that the heart rate/ST slope is better than standard electrocardiographic criteria for both the detection of coronary disease and the determination of the presence of triple vessel disease.[6] They acknowledged that highly selected populations of patients with known coronary disease or those with "normal" hearts were investigated. They did not provide data to demonstrate that the test is able to select prospectively patients with important coronary disease from a suspect population. They criticised other studies that did not find a good correlation between the slope and the extent of coronary disease,[4] generally because patients in the populations studied included a variable number who had had a previous myocardial infarction. The early reports from Leeds, however, did not mention whether or not the patients had had previous infarction[2] and since infarction was not a reason for exclusion there was presumably the usual admixture of patients.

On page 512 of this issue of the *British Heart Journal* the Leeds group report a group of patients with ischaemic heart disease. In two thirds of them the heart rate/ST slope failed to predict the severity of the demonstrated coronary artery disease. The Leeds workers suggest that this is because they were tested early after acute myocardial infarction. They say the underestimates were the result of left ventricular scarring producing less ischaemic myo-

Requests for reprints to Dr Raphael Balcon, The London Chest Hospital, Bonner Road, London E2 9JX.

cardium for a given stenosis. The overestimates were attributed to increased left ventricular volume, as judged by the cardiothoracic ratio, causing "more ischaemia" than would otherwise have occurred.

It may well be that the early response to exercise after infarction is modified by myocardial factors. These studies were usually performed 10 days to three weeks after the infarction and used submaximal testing.[7 8] Serial exercise testing after infarction has demonstrated that the findings change and for instance "ischaemic" ST depression at three weeks has a different prognostic significance than that occurring 11 weeks after infarction.[9] The patients reported were studied for a mean of >34 days after the acute myocardial infarction, which more closely resemble the "late" tests reported by others. It seems more likely therefore that these observations, which are in line with those of other workers, are the result of the expected variability of a biological system.

The controversy therefore remains. It is agreed by all, however, that the original high hopes that a non-invasive method of determining the exact extent of coronary disease had been found have not been realised. The mere fact that reliable investigations have been unable to reproduce the results casts considerable doubt on the value of the technique. Much emphasis has been laid on the need to follow the test protocol exactly but despite doing this at least one group still failed to confirm the findings.[4] The test cannot therefore be recommended at this stage for general use because there are doubts about its reliability and practical difficulties with both its performance and analysis.

References

1 Berenyi I, Hajduczki I, Boszormenyi E. Terheles alatti ST szakasz depressio quantitativ ertekeles a coronariabetegseg sulyossaganak megitelesere. *Cardiologica Hungarica* 1979;**8**:295–302.

2 Elamin MS, Boyle R, Kardash MM, *et al.* Accurate detection of coronary heart disease by new exercise test. *Br Heart J* 1982;**48**:311–20.

3 Quyyumi AA, Raphael MJ, Wright C, Bealing L, Fox KM. Inability of the ST segment/heart rate slope to predict accurately the severity of coronary artery disease. *Br Heart J* 1984;**51**:395–8.

4 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary angiographic findings. *Br Heart J* 1984;**52**:304–7.

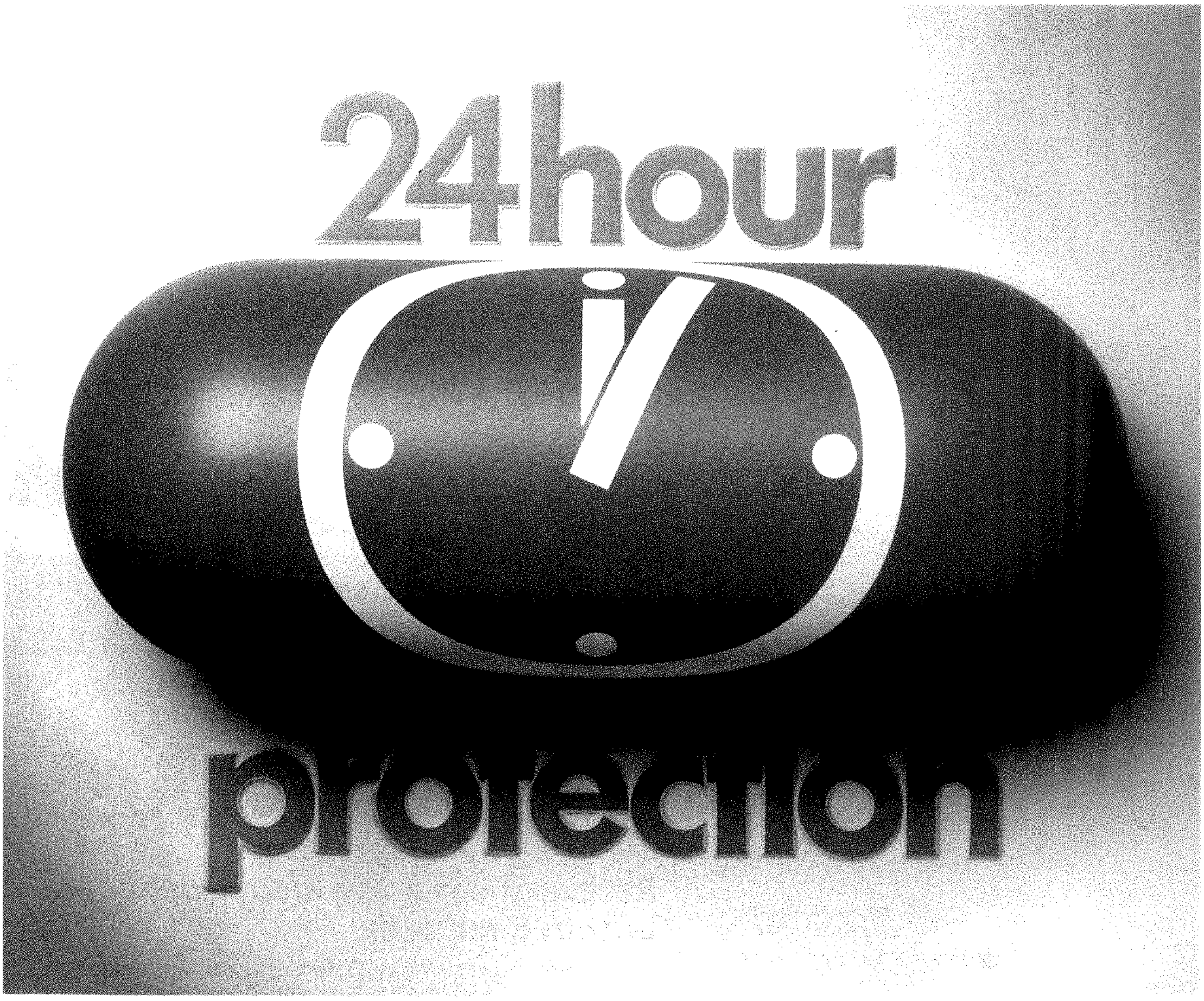
5 Okin PM, Kligfield P, Amiesen O, Goldberg HL, Borer JS. Improved accuracy of the exercise electrocardiogram: identification of three-vessel coronary disease in stable angina pectoris by analysis of peak rate-related changes in ST segments. *Am J Cardiol* 1985;**55**:271–6.

6 Kligfield P, Okin PM, Amiesen O, Borer JS. Evaluation of coronary artery disease by an improved method of exercise electrocardiography: the ST segment/heart rate slope. *Am Heart J* 1986; **112**:589–98.

7 Jennings K, Reid DS, Julian DG. Role of early post-infarction exercise test in identifying candidates for early coronary surgery [Abstract]. *Br Heart J* 1983;**49**:289.

8 Sullivan ID, Davies DW, Sowton E. Submaximal exercise testing early after myocardial infarction: difficulty of predicting coronary anatomy and left ventricular performance. *Br Heart J* 1985;**53**:180–5.

9 Sami M, Kraemer H, DeBusk RF. The prognostic significance of serial exercise testing after myocardial infarction. *Circulation* 1979;**60**:1238–45.



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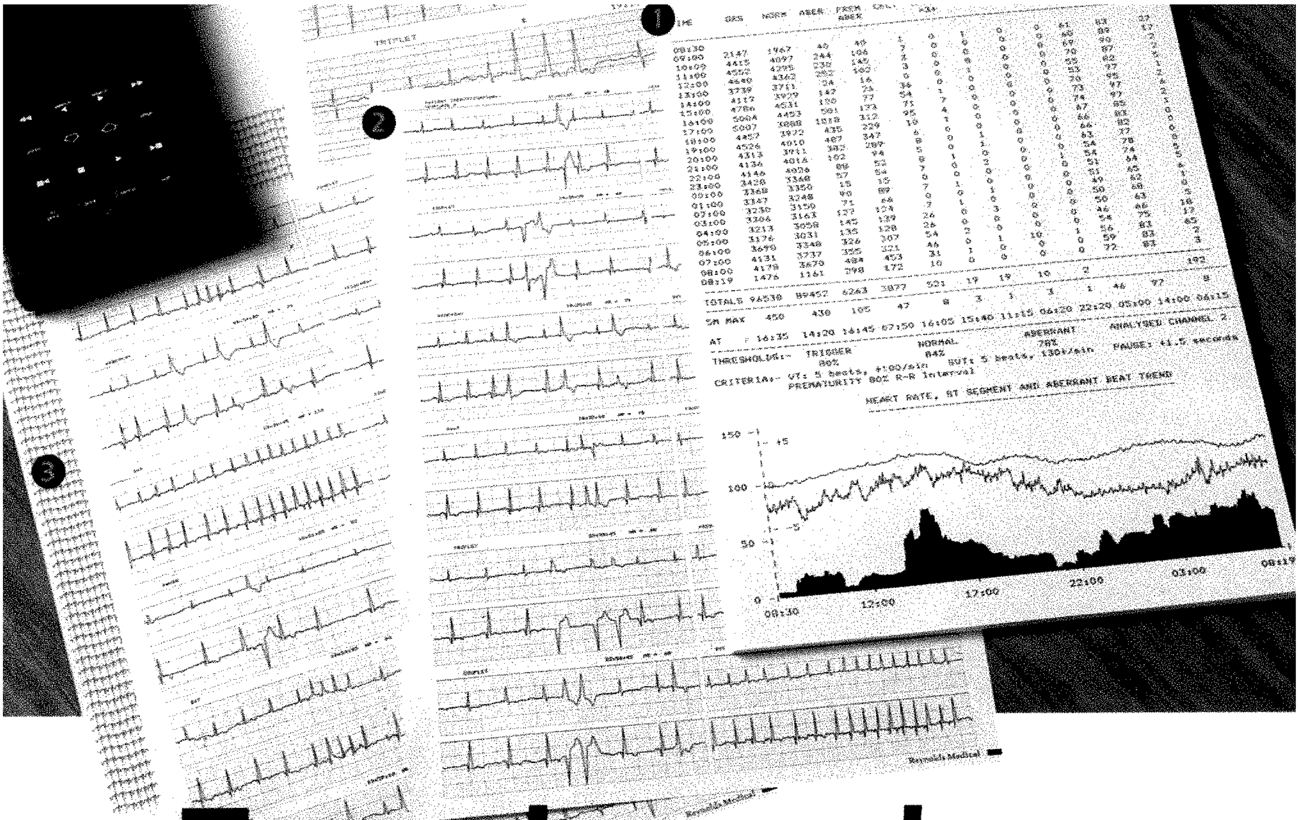
Use Control of mild to moderate hypertension. 'Inderal' LA and Half-'Inderal' LA are also indicated for angina, anxiety, essential tremor, thyrotoxicosis and prophyaxis of migraine. **Dosage and administration Hyperension** One capsule daily of 'Inderex' or one capsule daily of 'Inderal' LA increasing by increments of one capsule of Half-'Inderal' LA if required. **Other indications** One capsule daily of Half-'Inderal' LA increasing o the equivalent of 3 capsules daily if required. **Elderly patients** Start with one capsule daily Half-'Inderal' LA. **Contraindications** Heart block; bronchospasm; after prolonged fasting; and in metabolic acidosis. Additionally for 'Inderex': anuria; renal failure; sensitivity to thiazides. **Precautions** Untreated cardiac failure: bradycardia. Treatment modifies tachycardia of hypoglycaemia. Transference from, or discontinuance of, clonidine. Prescription of Class I antidysrhythmic agents. Co-administration with verapamil. Anaesthesia. Pregnancy. Cessation of beta-blocker therapy should be gradual in patients with ischaemic heart disease. Additionally with 'Inderex': diabetes; hepatic cirrhosis with ascites; and co-administration of digitalis or lithium containing preparations. **Side effects** Cold extremities, nausea, insomnia, lassitude and diarrhoea are usually transient. Isolated cases of paraesthesia of the hands. Rashes and dry eyes have been reported with beta-blockers. Additionally with 'Inderex': hypokalaemia (especially in patients already potassium depleted): hyperuricaemia. Rare reports of rashes, necrotising vasculitis, acute pancreatitis, blood dyscrasias and aggravation of pre-existing myopia. **Product licence numbers and basic NHS cost** (28-day calendar pack) 'Inderal' LA (29/0128) £6.66; Half-'Inderal' LA (29/0173) £4.48; 'Inderex' (29/0157) £7.44. 'Inderal' LA, Half-'Inderal' LA and 'Inderex' are trademarks. Further information is available from: ICI Pharmaceuticals (UK), Alderley House, Alderley Park, Macclesfield, Cheshire SK10 4TF.



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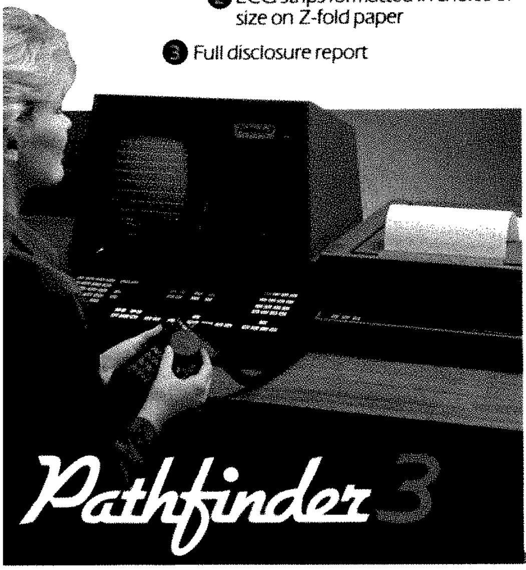

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The right way to automate arrhythmia detection

Br Heart J 1987;57:505–11

Medical treatment of patients with severe exertional and rest angina: double blind comparison of β blocker, calcium antagonist, and nitrate

A A QUYYUMI, T CRAKE, C M WRIGHT, L J MOCKUS, K M FOX

From the National Heart Hospital, London

SUMMARY The role of medical treatment of patients who had resting nocturnal angina as well as exertional angina was investigated. The effects of atenolol 100 mg a day, nifedipine 20 mg three times a day, and isosorbide mononitrate 40 mg twice a day were investigated in a double blind, triple dummy randomised study. Nine patients with coronary artery disease, early positive exercise tests, and transient daytime and nocturnal ambulatory ST segment changes were initially assessed off all antianginal medication. They were then treated with each drug for three five day periods. Angina diaries were reviewed and maximal treadmill exercise tests and 48 hour ambulatory ST segment monitoring were performed at the end of each treatment period. Resting and exercise heart rate and blood pressure were significantly lower on atenolol than on either isosorbide mononitrate or nifedipine. The duration of exercise to 1 mm ST segment depression was significantly greater on atenolol than on isosorbide mononitrate. Only one patient had an improvement in exercise tolerance on nifedipine that was greater than the improvement on atenolol; this patient had single vessel disease. The total number and duration of episodes of ST segment change during ambulatory monitoring were significantly lower with atenolol than on either isosorbide mononitrate or nifedipine. Nocturnal ST segment changes were abolished in six patients on atenolol, in six patients on nifedipine, and in five patients on isosorbide mononitrate. When nocturnal ST segment changes occurred, their frequency was reduced with all three drugs. Pain was abolished in four patients on atenolol and pain relief was significantly better on atenolol than on isosorbide mononitrate. There was no significant difference in pain relief between isosorbide mononitrate and nifedipine.

Thus β receptor blockade with atenolol was the most effective means of reducing myocardial ischaemia both during exercise and at rest at night without causing deterioration in any patient. Nocturnal myocardial ischaemia in patients with severe coronary artery disease can be effectively treated with β receptor antagonists and vasodilators.

Angina and myocardial ischaemia can occur on exertion or at rest in the same individual at different times of the day and night.[1] Different pathophysiological mechanisms have been used to explain ischaemia occurring at rest and on exertion in patients with obstructive coronary artery disease. Exertional angina is believed to be the result of myocardial oxygen demand exceeding supply, but angina at rest and at night is considered to be due to reduction in coronary blood flow caused by factors such as coronary spasm[2 3] and platelet aggregation.[4] Thus if treatment is to be tailored to symptoms β adrenoceptor antagonists should be recommended for ischaemia on exertion, and vasodilators, such as nitrates or calcium antagonists, should be used for rest angina. Recently, there has been evidence that ischaemia at rest and at night tends to occur mainly in patients with severe forms of coronary artery disease and that heart rate often increases before the onset of ischaemia in these patients.[5] In patients with normal coronary arteries or minor disease who develop ischaemia due to localised coronary spasm,

Requests for reprints to Dr A A Quyyumi, National Heart Hospital, Westmoreland Street, London W1M 8BA

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however, there are no increases in the indices of myocardial oxygen consumption before the onset of ischaemia.[6] It is therefore crucial to determine the ideal treatment for patients with coronary artery disease who have evidence of exertional and rest angina.

Several studies with ambulatory ST segment monitoring have demonstrated the occurrence of painless as well as painful ischaemia during daily activities.[7 8] It is therefore important to perform ambulatory ST segment monitoring during assessment of antianginal agents as this not only provides information on the frequency of ischaemia occurring during normal daily activities, but also demonstrates painless episodes of myocardial ischaemia. In this study we have used ambulatory ST segment monitoring to assess the effects of standard antianginal treatment with a β adrenoceptor antagonist (atenolol), a calcium antagonist (nifedipine), and a nitrate (isosorbide mononitrate) in patients with frequent exertional daytime and nocturnal resting angina pectoris.

Patients and methods

PATIENTS

We studied nine patients, six men and three women, mean (SD) age 62 (7) years, with confirmed coronary artery disease and a history of both exertional and nocturnal angina pectoris and positive exercise tests (table 1). Three patients had had a previous myocardial infarction. One patient (case 2) had single left anterior descending coronary stenosis only, whereas all others had three vessel disease with or without left main stem stenosis. All patients were shown to have reversible ambulatory ST segment changes during the day and at rest at night while off antianginal medication. The patients' symptoms had been stable for at least two months before the study started and none had suffered a recent myocardial infarction.

STUDY PROTOCOL

All regular antianginal medication was withdrawn for 48 hours in hospital before the study began. Sublingual nitroglycerin was given for pain. The ST segment was monitored in ambulant patients for at least 24 hours and up to 48 hours (mean (SD) 35 (12) hours) (table 1). Patients who had reversible ST segment changes during the daytime and also at night (24.00 to 06.00 hours) were recruited into the study after giving informed written consent. The study was approved by the hospital ethics committee.

Three drugs, atenolol, nifedipine, and isosorbide mononitrate were administered for five days each in a double blind, randomised manner according to a latin square design with a triple dummy technique. Atenolol was given in a daily dose of 100 mg, isosorbide mononitrate 40 mg twice a day, and nifedipine was given three times at day at a dose of 10 mg for two days and 20 mg three times a day for three days to overcome the problems that occasionally arise with the higher dose of nifedipine.[9] Throughout the various treatment periods, patients used sublingual nitroglycerin tablets to relieve pain. Six patients were assessed in hospital throughout the study and the other three patients had drug treatment periods at home. Patients were instructed to be mobile in and around the hospital or at home during the drug treatment periods. During the initial in hospital assessment period when all antianginal medication was discontinued, patients were advised not to undertake full activity in order to avoid frequent pain. The purpose of this part of the study was to identify patients with ST segment changes at night and at rest.

At the end of each treatment period, patients had ambulatory ST segment monitoring for 48 hours and kept angina diaries. Routine treadmill exercise tests were performed at the end of each five day treatment period.

Table 1 *Severity of coronary artery disease and the number and duration of painful and painfree episodes of ST segment change during the day and night during 24 hour ambulatory ST segment monitoring in patients who were off all antianginal medication*

Patient	*Type of coronary artery disease*	*Total episodes*	*Nocturnal episodes*	*Total duration (min)*	*Number of painful episodes*
1	3	7	2	473	2
2	1	11	3	446	0
3	3	11	1·5	316	2
4	3	13	2·5	127	6·5
5	3	11	3	133	4
6	3	2	1	55	2
7	3	12	3	125	4
8	3	8·5	1	264	1
9	3	6	2	150	4
Mean (SD)		9·1 (3·5)	2·1 (0·8)	228 (160)	2·7 (1·9)

AMBULATORY ST SEGMENT MONITORING

ST segment monitoring was performed with the Oxford Medilog II frequency modulated recorders which give good reproduction of low frequency (0·05 – 40 Hz <3 dB down) electrocardiographic signals. The bipolar lead CM5 was recorded continuously for 24–48 hours, initially with the patient off all medication and then at the end of each drug treatment period. The tapes were analysed at 60 times normal speed on the Oxford Instruments MA 20 analyser and the time, duration, and maximum magnitude of ST segment depression or elevation during each episode were noted. The heart rate at the onset of ST segment change was also noted for each episode. Significant ST segment depression was defined as a shift of 1 mm or greater in magnitude 0·08 seconds after the J point that persisted for at least 30 seconds. Significant ST elevation was defined as a shift of the J point of ⩾1 mm that persisted for more than half a minute. The number, duration, and maximum magnitude of episodes were measured. The number of nocturnal, painful, and painfree episodes were also noted in each treatment period.

EXERCISE TESTING

Symptom limited maximal exercise tests were performed by all patients at the end of each five day treatment period according to the modified Bruce protocol. Patients had had at least two previous exercise tests before the study began. Significant ST segment depression was defined as a planar or downsloping shift of the ST segment of ⩾1 mm 0·08 seconds after the J point. Tests were terminated if ST segment depression of ⩾2 mm occurred with or without pain or if severe chest pain, hypotension, arrhythmias, or exhaustion developed. The heart rate, systolic blood pressure, and rate-pressure product were measured at rest and at the onset of 1 mm ST segment depression during each treatment period and the duration of exercise to 1 mm ST segment depression was noted.

STATISTICAL ANALYSIS

The different drug treatment periods were compared by analysis of variance. When the f value was significant, a paired *t* test was used to compare treatments.

Results

During the initial assessment period all patients had reversible episodes of ST segment change—ST depression in eight and ST elevation in one—both during the day (mean (SD) 9·1 (3·5) episodes) and at rest at night (mean (SD) 2·1 (0·8)) during each 24 hour period (table 1). Only a mean of 30% of episodes were accompanied by pain. One patient (case 2) could not tolerate isosorbide mononitrate because of headaches and nausea and another patient (case 7) could not tolerate nifedipine because headaches occurred even at a lower dose. In these two patients assessment was limited to only two drugs.

HEART RATE

The heart rate throughout the day and night was significantly ($p < 0·01$) lower on atenolol than during the initial assessment period when patients were off all antianginal medication or when they were treated with nifedipine or isosorbide mononitrate. The heart rate on nifedipine and isosorbide mononitrate, however, was not significantly different either during the day or at night from that during the initial assessment period when all antianginal medication was discontinued.

EXERCISE TEST

Table 2 shows the duration of exercise to 1 mm ST segment depression during the different drug treatment periods. The mean duration of exercise to

Table 2 *Rest and exercise haemodynamic function and duration of exercise to 1 mm ST segment depression during different drug treatment periods. Values given are mean (1SD)*

				p value		
	Atenolol	*Nifedipine*	*Isosorbide mononitrate*	*Atenolol vs nifedipine*	*Atenolol vs isosorbide mononitrate*	*Nifedipine vs isosorbide mononitrate*
Rest						
Heart rate (beats/min)	60 (13)	91 (14)	86 (12)	0·01	0·01	NS
Systolic blood pressure (mm Hg)	130 (28)	142 (26)	149 (34)	NS	NS	NS
Rate-pressure product (× 10^3)	8 (3)	12·9 (3)	12·6 (4)	0·05	0·01	NS
1 mm ST depression:						
Heart rate (beats/min)	81 (11)	118 (28)	109 (17)	0·01	0·01	NS
Systolic blood pressure (mm Hg)	146 (31)	158 (28)	166 (38)	0·01	0·01	NS
Rate-pressure product	11·9 (3)	20·4 (7)	18 (4·8)	0·01	0·01	NS
Duration (min)	3·6 (0·9)	3·2 (2·7)	2·3 (1)	NS	0·01	NS

ischaemia was significantly greater with atenolol than with isosorbide mononitrate ($p < 0\cdot01$). When individual responses were analysed only one patient reached the same level of exercise before ST segment depression developed on both atenolol and isosorbide dinitrate, whereas all other patients achieved a greater workload with atenolol (fig 1). The mean workload achieved on nifedipine was 11% less in the group as a whole than that achieved on atenolol. In two patients similar workloads were achieved before ischaemia developed with the two drugs and one patient (case 2) reached a greater workload on nifedipine than on atenolol (fig 1). In the seven patients in whom treatment with both nifedipine and isosorbide mononitrate can be compared there was no significant difference in exercise duration between these drugs.

The mean resting heart rate was measured after the patient stood for two minutes before the exercise test. It was significantly lower on atenolol than on nifedipine (52%, $p < 0\cdot01$) or on isosorbide mononitrate (43%, $p < 0\cdot01$) (table 2). There was no difference in resting heart rate between nifedipine and isosorbide mononitrate ($p > 0\cdot05$). There was no significant difference between the resting systolic and diastolic blood pressure during the different treatment periods. The heart rate and double product (heart rate × systolic blood pressure) were both significantly lower at the time of onset of 1 mm ST segment depression during exercise testing on atenolol than on nifedipine ($p < 0\cdot01$) or isosorbide mononitrate ($p < 0\cdot01$) (table 2). During exercise there were no significant differences in these haemodynamic indices between the nifedipine and the isosorbide mononitrate treatment periods.

AMBULATORY ST SEGMENT MONITORING

Eight patients had episodes of ST segment depression only and one patient had episodes of ST segment elevation and depression. The total number and duration of episodes of ST segment change were significantly lower during treatment with atenolol than during treatment with nifedipine or isosorbide mononitrate (fig 2). Three patients had no episodes of ST segment change during treatment with atenolol. Comparison of individual responses on atenolol and on nifedipine showed that two patients had a similar number of episodes during both treatment periods but that the duration of episodes was reduced on atenolol. In all the other patients the number of episodes was greatly reduced on atenolol. Eight patients had fewer episodes of ST segment depression on atenolol than on isosorbide mononitrate. In the remaining patient the number of episodes of ST segment change on the two drugs was similar but their duration was greatly reduced on atenolol. Nocturnal ST segment changes recurred in only three patients on atenolol, in three patients on nifedipine, and in four patients during treatment with isosorbide mononitrate. The frequency and duration of nocturnal ST segment change were less

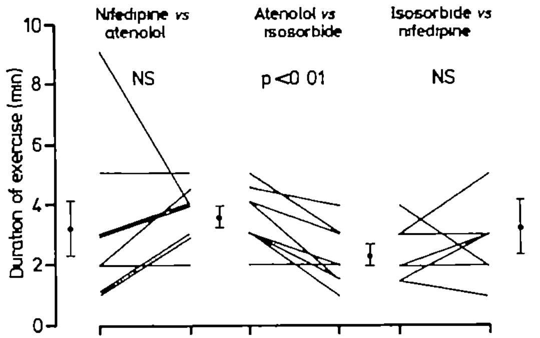

Fig 1 *Duration of exercise to 1 mm ST segment depression during different treatment periods. Individual patient responses and their means (1 SE) are shown.*

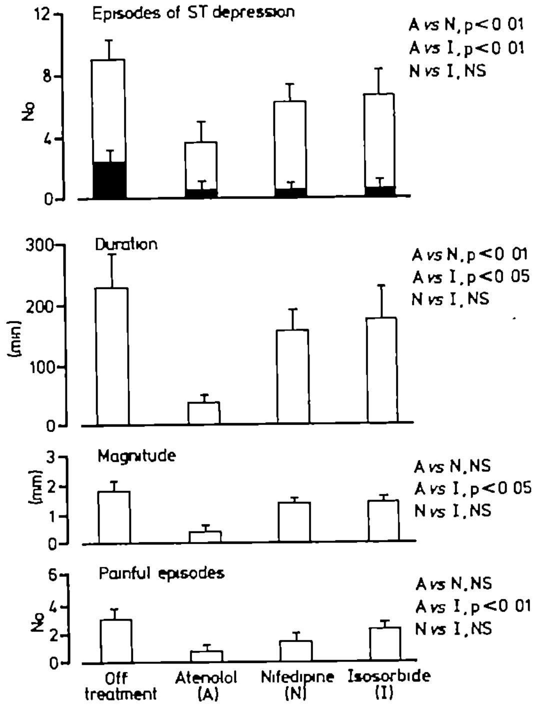

Fig 2 *Daily frequency of daytime and nocturnal (shaded columns) episodes of ST depression, their duration and magnitude, and the frequency of painful episodes during the initial off treatment period and during various treatment periods. Results are expressed as means (1 SE)*

during each treatment period than during the initial assessment period when patients were off all antianginal medication.

Pain was much less frequent on atenolol; four patients experienced no pain at all during the 48 hour monitoring period (fig 2). Two patients became pain free on nifedipine and five had less pain on atenolol than on nifedipine. Two patients experienced more pain on atenolol than on nifedipine, although the number of painfree episodes of ST segment change and their duration were greater on nifedipine. In all patients the frequency of pain on atenolol was significantly less than that experienced on isosorbide mononitrate (65%, $p < 0{\cdot}01$). There was no overall significant difference in pain frequency between isosorbide and nifedipine treatment periods ($p > 0{\cdot}05$).

ADVERSE EFFECTS

None of the patients had more episodes of angina during any of the three treatment periods than during the initial assessment period when they were off all antianginal medication. One patient was intolerant of nifedipine and one of isosorbide mononitrate and they were assessed on two drugs only.

Discussion

ST segment changes have been shown to be reliable indicators of underlying myocardial ischaemia[10 11] with the magnitude of change signifying either the size of myocardium affected or the severity of the ischaemia.[11] With the recent advent of frequency modulated recording systems it is possible faithfully to record and reproduce ST segment changes occurring during normal daily activities.[12] This technique provides an increased insight into the frequency of daily ischaemia experienced by a patient with angina. It not only detects painless episodes of myocardial ischaemia, but also demonstrates the duration and magnitude of each episode of ischaemia. Some patients develop ischaemia that is entirely painfree[1 13] and it is thus unreliable to depend totally on a patient's history of chest pain as an indicator of the frequency of myocardial ischaemia. Furthermore, the history does not always indicate the severity and duration of the ischaemic episode.[1] Ambulatory ST segment monitoring also allows the detection of ischaemia not only on exertion during the daytime but also at rest and at night.

There has been controversy about the pathophysiology of ischaemia that occurs at night and at rest. Several studies have demonstrated that ischaemia occurring at rest is secondary to factors which primarily reduce coronary blood flow, such as coronary spasm or platelet aggregation.[2–4 14] If this mechanism is important vasodilators such as nifedipine or isosorbide mononitrate would be expected to improve rest angina and ischaemia. Furthermore, β adrenoceptor antagonists theoretically may be contraindicated in these patients because they can increase coronary vascular resistance by direct β_1 receptor blockade and unopposed α receptor stimulation.[15] It is important to establish which form of medical treatment is most suitable for the considerable numbers of patients with severe coronary artery disease and frequent rest and exertional angina.

We compared the efficacy of three established antianginal agents, which are currently widely used and have diverse modes of action, in the treatment of patients with exertional and nocturnal angina. We also assessed whether any agent was likely to cause deterioration of myocardial ischaemia experienced during normal daily activities or at night. Atenolol is a β_1 selective receptor antagonist with no intrinsic sympathomimetic activity.[16] It has been shown to be an effective antianginal agent in placebo trials and as effective as other β receptor antagonists.[17] At a dose of 100 mg daily atenolol has significant negative chronotropic effects. In this study it reduced the heart rate and rate-pressure product not only at rest during the day and night but also on exercise. Thus, atenolol must have reduced myocardial oxygen consumption at rest and on exercise.

Nifedipine is a calcium channel blocking agent with no appreciable negative chronotropic effects.[18] Calcium antagonists are effective smooth muscle relaxants, causing not only peripheral arteriolar vasodilation but also coronary arterial dilatation.[19] Nifedipine is an effective antianginal agent not only in patients with exertional angina[20] but also in patients with variant angina and unstable angina.[21 22] Some studies, however, have demonstrated a variable response to nifedipine. Although patients improved at a lower dose of 30 mg a day they became worse at higher doses.[9] To overcome this we started all patients on 10 mg of nifedipine three times daily for the first two days and increased the dose to 20 mg three times daily thereafter. If no deterioration in symptoms occurred this dose was continued. Isosorbide mononitrate is more reliably and effectively absorbed from the gastrointestinal tract than isosorbide dinitrate.[23] Isosorbide mononitrate reduces ventricular end diastolic pressure and probably also has direct coronary arterial dilating action.[24 25] At a dose of 40 mg twice daily it was effective in improving the exercise haemodynamics and pain frequency in patients with angina pectoris.[26]

The results of ambulatory ST segment monitoring demonstrate that overall the patients improved most on atenolol in terms of the number, duration, and magnitude of episodes of myocardial ischaemia experienced. The effects of nifedipine and isosorbide mononitrate were not significantly different. The improvement on atenolol was not only striking with the daytime exertion related episodes but persisted during the episodes at rest at night. None of the patients experienced worsening of angina, either daytime or nocturnal, on atenolol.

Nocturnal ischaemia was improved on all three drugs; most patients did not experience nocturnal pain or ischaemia during any of the treatment periods. When it did recur, the frequency and duration of nocturnal ischaemia were less than during the initial assessment off all antianginal medication. This result indicates, firstly, that atenolol was effective not only in exertion related ischaemia but it also improved or abolished nocturnal resting angina without causing deterioration in any patient studied. Secondly, nocturnal resting ischaemia can also be treated effectively by the vasodilators nifedipine and isosorbide mononitrate which are, however, considerably less effective than atenolol for treating daytime exertion related angina. Finally, the mechanism of precipitation of nocturnal ischaemia in patients with severe coronary artery disease is likely to be multifactorial and a reduction of myocardial oxygen demand by β receptor antagonists is probably the most effective way of preventing ischaemia in this group of patients.

Most patients in this study had three vessel coronary artery disease, frequent angina, and greatly reduced exercise tolerance. In order to characterise the patients adequately, they were taken off all antianginal medication so that ambulatory monitoring could be performed. All patients had exertional angina and the purpose of this phase of the study was primarily to identify those patients who also had demonstrable nocturnal ischaemia. Patients were all admitted to hospital for this phase and advised not to undertake normal activity. This advice was likely to reduce exertion related ischaemia but would not be expected to influence resting or nocturnal ischaemia. For this reason, we have limited comparisons to the three double blinded treatment periods in this study because all these were performed in similar circumstances.

The only patient whose exercise response was most markedly improved with nifedipine had single vessel disease. This may be because this patient differed from the others in that an increase in vasomotor tone was an important mechanism in precipitating myocardial ischaemia—hence the good response to nifedipine and the relatively poor response to atenolol. Further investigations in this patient seemed to confirm this hypothesis as intravenous ergometrine produced pronounced localised coronary vasoconstriction.

Atenolol also increased the duration of exercise to ischaemia during conventional exercise testing more than isosorbide mononitrate did. Also only one patient reached a greater workload on nifedipine than on atenolol. As expected, the heart rate, blood pressure, and the rate-pressure product at rest were significantly lower on atenolol than on the two vasodilators. At the onset of 1 mm ST depression the heart rate and double product were lower on atenolol and remained significantly lower despite the duration of exercise being significantly longer on atenolol than on nifedipine or isosorbide mononitrate. This paradoxical reduction of the double product at peak exercise despite an improvement in exercise tolerance by β receptor antagonists has been reported before.[27 28] The apparently detrimental effects of raising end diastolic filling pressure and coronary vascular resistance produced by β blockers may explain why the same rate-pressure product is not reached before ischaemia develops.[29 30] Because all three drugs were beneficial in reducing the frequency of nocturnal angina and because their mechanisms of action are different, combination treatment of such patients may be appropriate.[20] None the less, the overall effect of atenolol in this study was an improvement in exercise tolerance and a considerable reduction in myocardial ischaemia during the day and night. Thus β receptor blockade, far from being contraindicated, is in fact of benefit in patients who have severe exertional and nocturnal angina caused by severe coronary artery disease.

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References

1 Quyyumi AA, Mockus L, Wright C, Fox KM. Morphology of ambulatory ST segment changes in patients with varying severity of coronary artery disease. Investigation of the frequency of nocturnal ischaemia and coronary spasm. *Br Heart J* 1985;53:186–93.

2 Maseri A, Severi S, De Nes M, *et al.* "Variant" angina. one aspect of a continuous spectrum of vasospastic myocardial ischemia: pathogenic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. *Am J Cardiol* 1978;42:1019–35.

3 Gorlin R. Role of vasospasm in the pathogenesis of myocardial ischemia and angina pectoris. *Am Heart J* 1982;103 598–603

4 Folts JD, Crowell EB Jr, Rowe GG. Platelet aggregation in partially obstructed vessels and its elimination with aspirin *Circulation* 1976,54:365–70.

5 Quyyumi AA, Wright CA, Mockus LJ, Fox KM Mechanisms of nocturnal angina pectoris: importance of increased myocardial oxygen demand

in patients with severe coronary artery disease. *Lancet* 1984;i:1207–9.

6 Guazzi M, Polese A, Fiorentini C, Magrini F, Olivari MT, Bartorelli C. Left and right heart haemodynamics during spontaneous angina pectoris. Comparison between angina with ST segment depression and angina with ST segment elevation. *Br Heart J* 1975;**37**.401–13

7 Quyyumi AA, Wright CM, Mockus LJ, Fox KM. How important is a history of chest pain in determining the degree of ischaemia in patients with angina pectoris? *Br Heart J* 1985;**54**:22–6.

8 Cecchi AC, Dovellini EV, Marchi F, Pucci P, Santoro GM, Fazzini F. Silent myocardial ischemia during ambulatory electrocardiographic monitoring in patients with effort angina. *J Am Coll Cardiol* 1983;**1**:934–9.

9 Deanfield J, Wright C, Fox K. Treatment of angina pectoris with nifedipine: the importance of dose titration. *Br Med J* 1983;**286**:1467–70

10 Samson WE, Scher AM. Mechanism of ST segment alteration during acute myocardial injury. *Circ Res* 1960;**8**:780–7.

11 Holland RP, Brooks H. TQ-ST segment mapping: critical review and analysis of current concepts. *Am J Cardiol* 1977;**40**:110–29.

12 Bragg-Remschel DA, Anderson CM, Winkle RA. Frequency response characteristics of ambulatory electro-cardiographic monitoring systems and the implications for ST segment analysis. *Am Heart J* 1982;**103**:20–31.

13 Schang SJ, Pepine CJ. Transient asymptomatic ST segment depression during daily activity. *Am J Cardiol* 1977,**39**:396–400.

14 Chierchia S, Brunelli C, Simonetti I, Lazzari M, Maseri A. Sequence of events in angina at rest: primary reduction in coronary flow. *Circulation* 1980,**61**:759–68.

15 Robertson RM, Wood AJJ, Vaughn WK, Robertson D. Exacerbation of vasotonic angina pectoris by propranolol. *Circulation* 1982;**65**:281–5.

16 Schwartz JB, Jackson G, Kates RE, Harrison DG. Long term benefit of cardioselective beta blockade with once daily atenolol therapy in angina pectoris. *Am Heart J* 1981;**101**:380–5.

17 Jackson G, Harry JD, Robinson C, Kitson D, Jewitt DE. Comparison of atenolol with propranolol in the treatment of angina pectoris with special reference to once daily administration of atenolol. *Br Heart J* 1978;**40**:998–1004.

18 Antman EM, Stone PH, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part 1. Basic and clinical electrophysiologic effects. *Ann Intern Med* 1980; **93**:875–85.

19 Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers and vascular smooth muscle. *Annu Rev Pharmacol Toxicol* 1977;**7**:149–66.

20 Lynch P, Dargie H, Krikler S, Krikler D. Objective assessment of antianginal treatment: a double blind comparison of propranolol, nifedipine and their combination. *Br Med J* 1980;**280**:184–7.

21 Muller JE, Gunther SJ. Nifedipine therapy for Prinzmetal's angina. *Circulation* 1979;**57**:137–9.

22 Hugenholtz PG, Michels HR, Serruys PW, Brower RW. Nifedipine in the treatment of unstable angina, coronary spasm and myocardial ischemia. *Am J Cardiol* 1981;**47**:163–73.

23 Abshagen U, Sporl-Radun S. First data on effects and pharmokinetics of isosorbide mononitrate in normal man. *Eur J Clin Pharmacol* 1981;**19**.423–9.

24 Bodigheimer K, Nowak FG, Delius W Vergleichende invasive Untersuchung uber die Wirking von Isosorbid-5-Moninitrat und Isosorbiddinitrat bei chronischer Herzinsuffizienz. *Med Welt* 1981; **32**:543–7.

25 Rafflenbeul W, Urthaler F, Russell RO, James TN, Lichtlen PR. Quantitative coronary angiography: effect of isosorbide dinitrate on coronary artery stenosis. In: Lichtlen PR, Engel HJ, Schrey A, Swan HJC, eds. *Nitrates III*. Berlin, Heidelberg, New York: Springer-Verlag, 1981:231–7.

26 Uberbacher HJ, Glocke M, Abshagen U Lanzeitvertraglichkeit und koronartherapeutische Wirksamkeit von Isosorbid-5-Mononitrat; offene Multicenter-Studie unter Praxisbending-ungen mit ISMO 20. *MMW* 1983;**125**:76–8.

27 Ho SWC, McComish MJ, Taylor RR. Effect of beta-adrenergic blockade on the results of exercise testing related to the extent of coronary artery disease. *Am J Cardiol* 1985;**55**:258–62.

28 Quyyumi AA, Wright C, Mockus L, Fox KM. Effect of partial agonist activity in beta blockers in severe angina pectoris: a double blind comparison of pindolol and atenolol. *Br Med J* 1984;**289**:951–3.

29 Gianelly RE, Treister BL, Harrison DC. The effect of propranolol on exercise induced ischemic S-T segment depression. *Am J Cardiol* 1969;**24**:161–5.

30 Sonnenblick EH, Braunwald E, Williams JF, Glick G. Effects of exercise on myocardial force-velocity relations in intact unanesthetised man: relative roles of changes in heart rate, sympathetic activity and ventricular dimensions. *J Clin Invest* 1965;**44**:2051–62

Br Heart J 1987;57:512–20

Use of the maximal ST/HR slope to estimate myocardial ischaemia after recent myocardial infarction

N BISHOP,* G HART,† R M BOYLE,† J B STOKER,† D R SMITH,* D A S G MARY*

*From the *Department of Cardiovascular Studies, University of Leeds, and †Killingbeck Hospital, Leeds*

SUMMARY Fifty two patients were examined 4–6 weeks after myocardial infarction to assess whether factors other than coronary artery narrowing affect the maximal ST/HR slope which is used as an index of myocardial ischaemia. The slope was compared with indices of myocardial scarring or cardiac enlargement derived from *x* ray and echocardiographic and angiocardiographic investigations. In 35 (67%) patients the slope failed to predict the severity of myocardial ischaemia attributable to coronary artery narrowing: in 14 (27%) patients the slope overestimated the findings of coronary angiography and in 21 (40%) patients the slope underestimated the findings of coronary angiography. In the remaining 17 (33%) patients the slope accorded with the assessment of myocardial ischaemia by coronary angiography. Underestimation by the slope was associated with significantly poorer left ventricular function and a lower ejection fraction, indicating a greater degree of myocardial scarring.

To assess whether overestimation was related to cardiac enlargement with better preservation of ventricular function a follow up examination was performed six months after infarction. In the overestimated group 11 patients were followed up and seven of them showed a reduction in the maximal ST/HR slope which correlated with a reduction in the cardiothoracic ratio. This suggested that cardiac enlargement had contributed to myocardial ischaemia.

The results suggest that if the maximal ST/HR slope is an index of exercise induced myocardial ischaemia after recent infarction, it is subject to the influences of coronary artery narrowing as well as those of scarring and cardiac enlargement.

Studies in Leeds have shown that the maximal ST/HR slope is an index of myocardial ischaemia when related to coronary artery narrowing in selected populations of patients with angina,[1 2] and that the slope is influenced by cardiac enlargement—for example in a selected population of patients with aortic valve disease and normal coronary arteriograms.[3]

In patients who have had an acute myocardial infarction exercise induced myocardial ischaemia has been related to coronary artery stenosis, though other factors, such as cardiac enlargement or the extent of myocardial scarring and muscle tissue loss, could be argued to affect the ischaemic process.[4–6] We report a comparison of the maximal ST/HR slope and the results of angiocardiography in patients with recent myocardial infarction as a further test of the reliability of the slope as an index of myocardial ischaemia.

Patients and methods

Consecutive patients were prospectively studied 4–6 weeks after myocardial infarction. The diagnosis of myocardial infarction was confirmed by the presence of at least two of the following criteria (*a*) typical history of chest pain lasting at least 30 minutes; (*b*) characteristic serial electrocardiographic changes, that is ST segment elevation, T wave inversion, and

Requests for reprints to Dr D A S G Mary, Department of Cardiovascular Studies, University of Leeds, Leeds LS2 9JT.

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the appearance of new Q waves; (*c*) a rise in serum creatine kinase to at least twice the upper limit of normal. Patients with complications after infarction—for example cardiogenic shock, cardiac failure, arrhythmias, or conduction disturbances occurring 72 hours after infarction; acute haemodynamic complications—for example mitral regurgitation, pulmonary embolism; and unstable angina were not considered for study. Patients with uncontrolled hypertension, concomitant valve or chronic cardiac disease, or other medical conditions making exercise difficult were excluded from study. No patient on digoxin was included in the study.

All patients gave informed consent to the investigations and the study was approved by the local ethics committee.

We examined the effects of myocardial scarring and cardiac enlargement on myocardial ischaemia early after infarction as assessed by the maximal ST/HR slope. Wall scarring was assessed by angiographic patterns of left ventricular wall motion[7] and ejection fractions. To assess the influence of cardiac enlargement patients were re-examined six months after infarction and individual changes in heart size were measured, with the patients acting as their own controls. Changes in cardiothoracic ratio were measured on standard chest *x* rays[8 9] and ventricular dimensions were obtained by cross sectional echocardiography.[10] A blind comparison was made between the maximal ST/HR slope and the results of angiocardiography, chest *x* rays, and echocardiography.

EXERCISE TEST

In each patient the exercise test was performed 4–6 weeks after a confirmed myocardial infarction. The details of the exercise test have been reported elsewhere.[11] Briefly, the exercise test was performed on an electrically braked bicycle ergometer with the patient in the upright position. Each test was preceded by a short preliminary exercise to determine the stepped increases in workload necessary to obtain stepped increases in heart rate of approximately 10 beats/minute, to enable adequate recordings by electrode replacement if required, and to familiarise the patient with the procedure. During the test the workload was increased every three minutes, with the test being terminated for the following reasons: anginal pain, ST segment depression > 0·3 mV, more than six multifocal ectopic impulses per minute or tachycardia, a decrease in blood pressure, or exhaustion.

The electrocardiogram was recorded from 13 leads—12 conventional leads and a bipolar lead (CM5)—with an ink jet Mingograph recorder (Siemens type 62). The leads were calibrated by setting the amplifier gain so that a 1 mV signal caused a displacement of 10 mm. Records from the 13 electrocardiographic leads were obtained at rest, during the last minute of each exercise step, and for at least five minutes after the end of exercise. The electrocardiogram was monitored throughout the test and recovery period. Systemic blood pressure was measured before, during the third minute of each exercise step, and during the recovery period.

The ST segment level was measured at a point 80 ms after the end of the QRS complex; a line drawn between consecutive PR segments was taken as the zero reference. This measurement was made with a magnifying glass fitted with a graticule marked in 0·1 mm divisions. The heart rate (beats/minute) was calculated by measuring the R–R interval on the electrocardiogram.

The measurements of ST segment level and heart rate were made from electrocardiographic records obtained during the steady state (heart rate value within ±5% of the mean) attained during the third minute of each exercise step. The values of heart rate and ST segment level were taken as the average value measured in at least 10 consecutive cardiac cycles obtained from records of all 13 electrocardiographic leads.

The maximal ST/HR slope was derived by performing regression analysis on the relation between the ST segment level and heart rate in each of the 13 electrocardiographic leads. In each lead the steepest slope of the computed regression lines which showed a linear regression was noted. The maximal ST/HR slope of all the 13 electrocardiographic leads was used as an index of myocardial ischaemia and this has units of mm per beat minute per 1000.[1 11]

ANGIOCARDIOGRAPHY

In each patient within one week of the exercise test selective coronary arteriography and left ventriculography were performed and reported on by the cardiologists without knowledge of the results of the exercise test.

Significant coronary artery disease was defined as luminal narrowing of the diameter of > 75% in any of the three major coronary arteries.[12] We used the same method of scoring angiograms so that we could compare the results of our study with previous studies in patients with angina.[11 12] Percentage narrowing was assessed by a visual impression based on views of the vessels in more than one plane. The degree of stenosis of a long lesion was estimated at its narrowest point and in vessels that contained more than one lesion the degree of stenosis was that of the most severe lesion. Patients were divided into four groups: those with no significant coronary artery disease and those with single, double, and triple vessel disease. Significant narrowing of the left main coronary artery was considered to be equivalent to significant narrowing of its two major branches and hence was labelled double vessel disease.

Assessment of the left ventricular function from ventriculography was made by visual impression. The left ventricular angiogram was scored on a scale of 0 to 4. The score was intended as an index of the degree of scarring and thus took account of the mobility and dilatation of the left ventricle[13]—a score of 0 being equivalent to normal left ventricular function and a score of 1 indicating mild impairment of left ventricular function with a range up to a score of 4 for severe impairment of left ventricular function.

Ejection fractions and end systolic and end diastolic areas and volumes were subsequently obtained from digitised tracings taken from the end systolic and end diastolic frames from the left ventricular angiogram.[14] These volumes were derived from single plane left ventricular angiography in the right anterior oblique view at 30° to the vertical.

To compare the ventricular areas and volumes of the patients studied we used the diameter of the cardiac catheter as a scale and adjusted measurements accordingly. Ejection fraction was calculated from:

$$\frac{\text{End diastolic volume—end systolic volume}}{\text{End diastolic volume}}$$

Volume measurements from single plane angiography may not be precise in patients with myocardial infarction. In this study these measurements were intended as a further index of scarring for group comparison.

ASSESSMENT OF CHANGES IN CARDIAC SIZE

Cardiothoracic ratio

All patients had a posteroanterior chest *x* ray taken in the erect position and in deep inspiration within a week of the exercise test soon after infarction and on the same day as their follow up exercise test. The cardiothoracic ratio was obtained in the usual way by dividing the transverse diameter of the heart by the internal diameter of the chest.[8 9]

Echocardiography

Left ventricular size was assessed by cross sectional echocardiography (Ultraimager, Honeywell). From the video recording of the echocardiographic examination the cross sectional areas of the left ventricle at end diastole in both the short axis view at the level of the papillary muscles and in the long axis apical four chamber view were measured, as was the long axis of the left ventricle.

Statistical analysis

Student's unpaired *t* test, correlation, and χ^2 testing were used as appropriate.

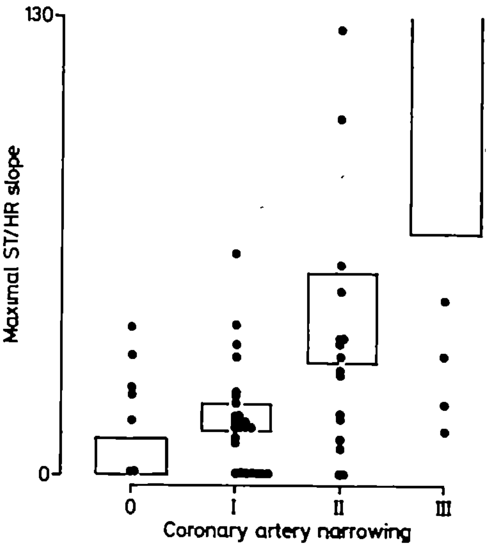

Fig 1 *Comparison of individual maximal ST/HR slope values (mm per beat min per 1000) with independent assessment of myocardial ischaemia from coronary angiography. The boxed areas indicate the equivalent slope values for that degree of coronary artery narrowing (0 = no significant stenosis, I = single vessel, II = double vessel, and III = triple vessel disease) previously found in a selected population with angina.*[1]

Results

CLINICAL DETAILS

Fifty three consecutive patients prospectively underwent exercise testing 24–44 (mean 34·7) days after a confirmed myocardial infarction. One of these patients was excluded from the study because we could not obtain an electrocardiogram that was adequate for the derivation of the maximal ST/HR slope. Blind comparison of the value of the maximal ST/HR slope and the findings of angiocardiography was made in 52 patients (six women, 46 men; aged 37–64 (52·6) years).

Twenty eight patients suffered an inferior myocardial infarction and in the remaining 24 patients there was an anterior infarction. Eight patients gave a history of previous myocardial infarction. At the time of examination the following drugs were being taken: β blocker (18 patients), thiazide diuretic (13 patients), frusemide (2 patients), nitrates (6 patients), nifedipine (2 patients), and methyldopa (1 patient). Twenty patients were receiving no drug treatment. In most patients followed up at six months there had been no change in drug treatment. Three patients were on additional vasodilator treatment (nifedipine or nitrates) which may increase the slope.[15 16]

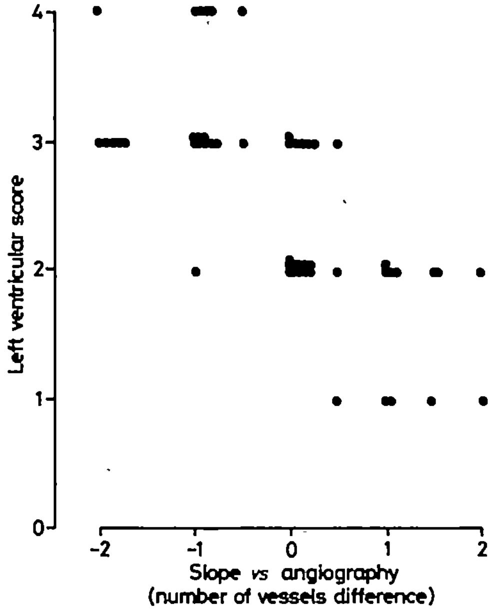

Fig 2 *Individual discrepancies between the assessment of myocardial ischaemia by the maximal ST/HR slope and by coronary angiography (in terms of the number of vessels difference) (mm per beat min per 1000) related to left ventricular score.*

For instance if the slope suggested single vessel disease and angiography showed double vessel disease, this would give a difference of −1. If angiography demonstrated single vessel disease and the slope value suggested double vessel disease, this would give a difference of +1. Where the slope gave intermediate values, say between single vessel and double vessel disease, this is taken as 1·5 for the purpose of comparison with angiography.

COMPARISON BETWEEN THE VALUE OF THE MAXIMAL ST/HR SLOPE AND THE ANGIOGRAPHIC EXTENT OF CORONARY ARTERY NARROWING

The maximal ST/HR slope increased as the severity of ischaemia worsened (fig 1). Eight patients had values of the slope in between the previously described discrete categories for no significant disease, single, double, and triple vessel disease. There was agreement between coronary angiographic assessment of the severity of myocardial ischaemia and the slope in only 17 (33%) of the 52 patients. In the remaining 35 (67%) patients the slope failed to predict the severity of myocardial ischaemia; the slope either underestimated the angiographic extent of significant coronary artery narrowing (21 patients (40%)) or it overestimated the angiographic extent of coronary artery narrowing (14 patients (27%)). No patient with significant narrowing of all three coronary arteries had a maximal ST/HR slope equivalent to triple vessel disease.

Because the underestimation of the extent of coronary artery disease could be due to the effect of myocardial scarring,[6] we examined indices of left ventricular function (the left ventricular score and ejection fraction).

LEFT VENTRICULAR FUNCTION

Left ventricular score

For patients given a left ventricular score of 4, indicating severe left ventricular dilatation and severe impairment of wall mobility, the value of the slope consistently underestimated the extent of coronary artery narrowing (fig 2). While for those patients judged to have the best preserved left ventricular function—that is with a left ventricular score of 1—the slope consistently overestimated the extent of coronary artery narrowing (fig 2). There is a tendency for a discrepancy between the slope and angiography to be more likely if the left ventricular score is high; linear regression analysis showed that this trend is significant ($r = -0{\cdot}68$, $p < 0{\cdot}001$) (fig 2).

A higher left ventricular score is significantly associated with larger end systolic and larger end diastolic volumes, and a lower ejection fraction (fig 3).

Left ventricular volumes

Underestimation by the maximal ST/HR slope of the severity of coronary artery narrowing is associated with larger end systolic and end diastolic volumes (table). Similar results were obtained when we used left ventricular areas derived from single plane angiography.

Ejection fraction

Underestimation by the maximal ST/HR slope is associated with a lower ejection fraction (fig 4; $r = 0{\cdot}60$, $p < 0{\cdot}001$).

In patients with single vessel disease there is a significant tendency between the value of the maximal ST/HR slope and the left ventricular score ($r = -0{\cdot}63$, $p < 0{\cdot}05$), lower values of the slope being associated with higher scores (fig 5). A trend is seen when the value of the slope is related to the ejection fraction ($r = +0{\cdot}57$, $p < 0{\cdot}05$).

FOLLOW UP STUDY

Of the total of 52 patients, 44 were re-examined six months after infarction; three had died, one had an embolic stroke, one had undergone coronary artery surgery, one had required permanent pacing for sinuatrial disease, and two patients declined further exercise tests.

All three patients who died had poor left ventricu-

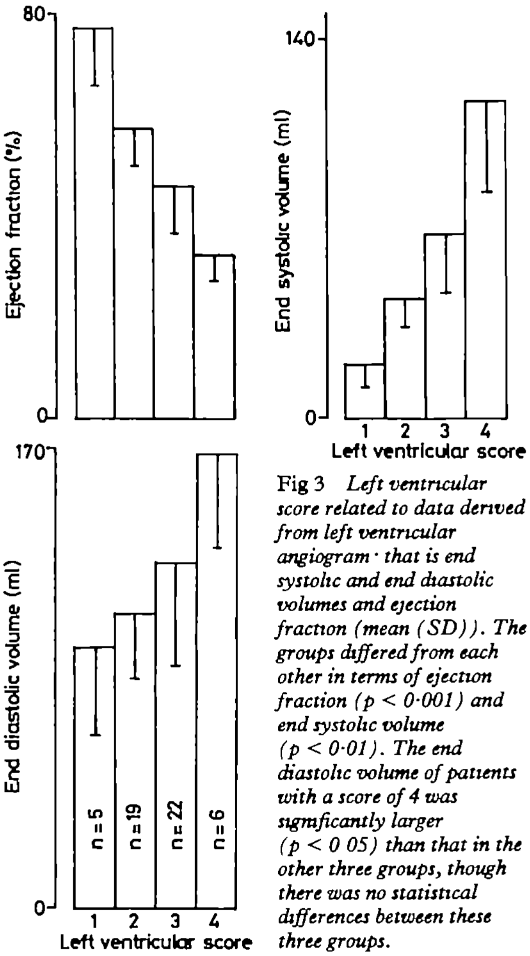

Fig 3 *Left ventricular score related to data derived from left ventricular angiogram: that is end systolic and end diastolic volumes and ejection fraction (mean (SD)). The groups differed from each other in terms of ejection fraction (p < 0·001) and end systolic volume (p < 0·01). The end diastolic volume of patients with a score of 4 was significantly larger (p < 0·05) than that in the other three groups, though there was no statistical differences between these three groups.*

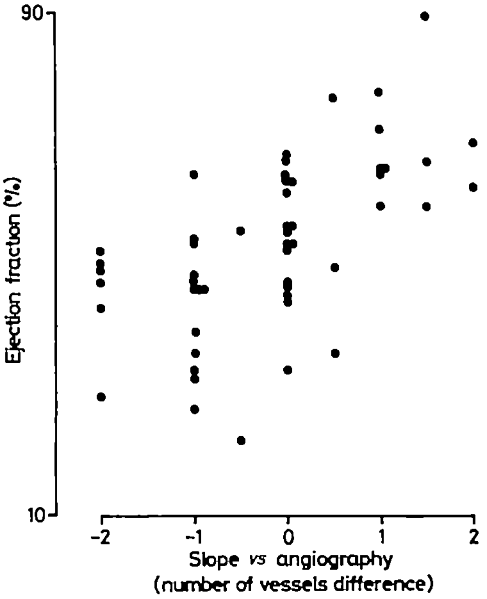

Fig 4 *Individual discrepancy between assessment of myocardial ischaemia by the maximal ST/HR slope (mm per beat min per 1000) and by coronary angiography (in terms of the number of vessels difference) in relation to ejection fraction.*

lar function (left ventricular scores of 3, 4, and 4; ejection fractions of 53, 27, and 29% respectively) and in all three the slope underestimated the severity of coronary artery narrowing.

To assess the influence of cardiac enlargement early after myocardial infarction we re-examined patients at six months and examined individual changes in heart size in relation to individual changes in the severity of myocardial ischaemia as assessed by the maximal ST/HR slope. In the 44 patients re-examined at six months there was a statistically significant reduction in cardiothoracic ratio (p < 0·02) from an initial mean (SD) value of 48·5 (4·5)%. The reductions in heart size as assessed by the cardiothoracic ratio were greater in the overestimate group, though this difference from the agreement and underestimate groups is not statistically significant.

Table *Ejection fraction and left ventricular volumes (mean (SD) (range)) for the three groups of patients in whom the maximal ST/HR slope showed either overestimation or underestimation or agreement with the findings of coronary angiography*

	Overestimation (n = 14)	*Agreement (n = 17)*	*Underestimation (n = 21)*
Ejection fraction (%)	64·8 (12·6) (36–89)	54·4 (9·3)* (33–67)	43·7 (10·5)†‡ (22–64)
End diastolic volume (ml)	107·4 (28·2) (72–146)	107·5 (29) (75–165)	141·7 (44·4)§ (78–230)
End systolic volume (ml)	39·1 (17·0) (10–68)	49·5 (20·2) (33–111)	81·7 (34·8)†‡ (32–180)

*Overestimate *vs* agreement, p < 0·02.
†Overestimate *vs* underestimate, p < 0·001.
‡Agreement *vs* underestimate, p < 0·01.
§Agreement or overestimate *vs* underestimate, p < 0·02

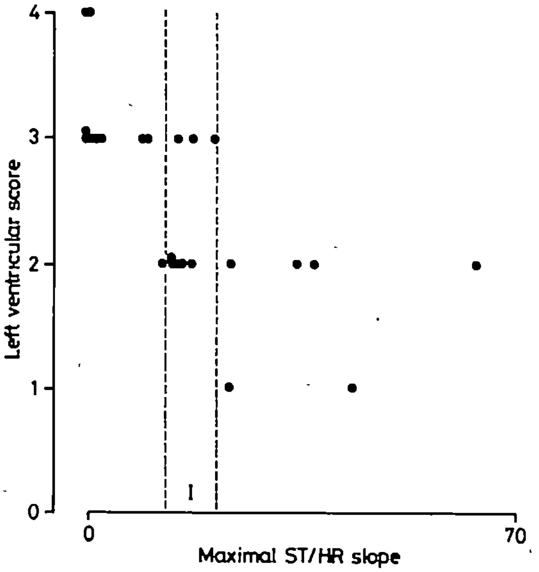

Fig 5 *Individual values of the maximal ST/HR slope (mm per beat min per 1000) related to left ventricular score for the 25 patients with single vessel disease. The range of the slope for single vessel (I) disease as found in selected patients with angina[1] is shown by the broken lines.*

Eleven of the 14 patients in whom the slope had overestimated the extent of coronary artery narrowing were re-examined at six months. Eight of these 11 patients showed a reduction in heart size as assessed by the cardiothoracic ratio. Seven of these eight patients had an associated reduction in the maximal ST/HR slope (fig 6). In contrast, such a correlation between a reduction in cardiothoracic ratio and the maximal ST/HR slope over a period of six months was found only in one of the 18 patients from the underestimate group who were re-examined (χ^2, $p < 0·01$).

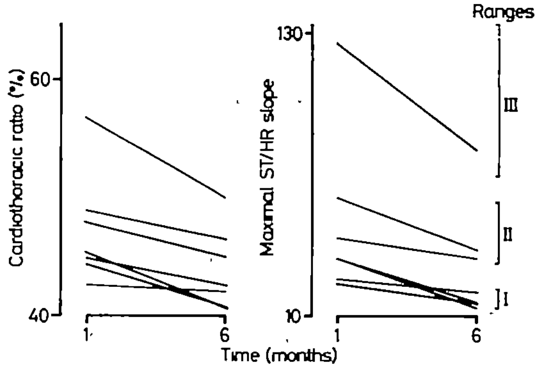

Fig 6 *Individual changes in cardiothoracic ratio and maximal ST/HR slope (mm per beat min per 1000) for seven patients from the group in which the slope overestimated the findings of coronary angiography. The ranges of the maximal ST/HR slope equivalent to single vessel (I), double vessel (II), or triple vessel disease (III), as obtained in selected patients with angina,[1] are given on the right of the figure.*

Of the 17 patients examined by echocardiography we had adequate images for measurement of left ventricular areas at end diastole in eight. The change in cardiothoracic ratio for these eight patients correlated with the change in the cross sectional end diastolic area of the left ventricle obtained from the apical four chamber view on cross sectional echocardiography ($r = 0·79$, $p < 0·02$).

Discussion

MAXIMAL ST/HR SLOPE AS INDEX OF MYOCARDIAL ISCHAEMIA

The maximal ST/HR slope has been proposed as an index of myocardial ischaemia.[1] In trials of hospital patients presenting with angina in Leeds, it was shown that the slope was 96·5% successful in detecting significant coronary artery stenosis[2] (as defined above). These patients were selected; they did not have left ventricular aneurysm, or conditions causing cardiac enlargement—for example valvular heart disease—and they were not examined within six months of myocardial infarction.

In a subsequent trial, patients with aortic valve disease and cardiac enlargement were examined.[3] In the absence of coronary artery narrowing cardiac enlargement was associated with values of the maximal ST/HR slope equivalent to coronary heart disease.[3] Left ventricular dilatation and hypertrophy is a reported cause of myocardial ischaemia.[4]

Attempts to reproduce the accuracy found in Leeds have to date been unsuccessful[17-19]; the reason for this is not known. It may be related to the characteristics of the patients studied, use of different techniques, and differences in angiographic interpretation. Other studies of the ST segment and heart rate relation that used different techniques and different angiographic criteria have suggested that this index provides a reliable assessment of the presence and severity of coronary disease in patients with angina.[20-22] False positive results have been reported in patients with aortic regurgitation[23] and false negative results in patients with previous myocardial infarction.[22,23]

This evidence suggests that the ability of the maximal ST/HR slope to detect any one cardiac or coronary lesion that leads to myocardial ischaemia must depend on the characteristics of the selected population being studied. Patients early after myocardial infarction could have, in addition to any coronary narrowing, cardiac lesions, such as enlargement or scarring, that influence myocardial ischaemia. For instance, left ventricular wall scarring and loss of myocardium may limit myocardial ischaemia whereas cardiac enlargement with a better preserved myocardium may predispose to myocardial ischaemia.[4-6] The present trial was planned to examine the effects of these factors on the maximal ST/HR slope, which is used as an index of myocardial ischaemia. We used the same techniques in assessing the maximal ST/HR slope that were used in previous studies[11 12] so that we could compare the results of the present trial with those of earlier ones.

FINDINGS OF THE PRESENT STUDY

The present findings suggest that coronary artery narrowing, myocardial scarring, and cardiac enlargement may affect the maximal ST/HR slope after recent myocardial infarction. Myocardial scarring would be associated with left ventricular dilatation, accompanied by an increase in end systolic volume, and reduced wall mobility. The left ventricular score was used as an index of scarring; the finding of an association between high scores and larger left ventricular volumes and a lower ejection fraction (fig 3) confirms that the score was an adequate, though crude, index of scarring. Underestimation of the findings of coronary angiography by the maximal ST/HR slope was found to be significantly associated with the index of myocardial scarring; namely, higher left ventricular scores (fig 2), and also with larger left ventricular volumes and a lower ejection fraction (table 1 and fig 4).

It could be argued that two "opposing" areas of myocardial ischaemia could be cancelling out their electrocardiographic manifestations, though there is no evidence for such an effect from experience with the maximal ST/HR slope in patients with angina.[1] The ST segment elevation associated with aneurysm formation could also be said to mask the presence of ischaemia, though aneurysms may be regarded as mainly representing scar tissue and would be included in the index of scarring used. In the present study many of the patients who had a maximal ST/HR slope of zero had significant narrowing of only the infarct related coronary artery, and this was often associated with poor left ventricular function and in some with aneurysm formation.

One of the principal determinants of prognosis in patients after myocardial infarction is the extent of myocardial damage—a larger infarct being associated with a poorer prognosis.[24] Though the number of patients in the present study is too small for adequate statistical analysis, the patients in whom the slope underestimated the angiographic extent of coronary artery narrowing had the highest mortality—all three patients who died came from this group. All these findings suggest that scarring may limit myocardial ischaemia as assessed by a functional index, the maximal ST/HR slope.

In this study larger left ventricular volumes were associated with indices of a greater degree of myocardial scarring. The above findings also suggest that scarring may limit myocardial ischaemia. In patients with well preserved left ventricular function—that is less scarring—it may be possible to demonstrate the effect of cardiac enlargement on myocardial ischaemia.

The influence of cardiac enlargement was assessed by correlating individual changes in heart size in the six months after myocardial infarction with changes in the maximal ST/HR slope. The cardiothoracic ratio is an accepted measure of change in heart size in an individual,[9] though it is not accurate for comparisons between patients. In this study correlation with echocardiographic measurements showed that changes in cardiothoracic ratio reflected alterations in left ventricular dimensions. Examination of these indices showed that there was evidence that ventricular size affected the maximal ST/HR slope.

In the group in which the slope overestimated left ventricular damage (that is those with the best preserved left ventricular function) most patients demonstrated a reduction in cardiothoracic ratio which was associated with a reduction in the maximal ST/HR slope. The reduction in the slope exceeded the 95% tolerance limits of obtaining the slope,[1] and for some patients involved a shift from the range of double vessel disease to single vessel disease.

In this study we obtained values of the slope that were intermediate between the categories of single and double vessel disease and double and triple vessel disease. It is our experience that such values are often obtained when cardiac enlargement has been evident.[3]

Even in the face of factors such as scarring and cardiac enlargement that influence myocardial ischaemia there was still a tendency for the assessment of myocardial ischaemia by the maximal ST/HR slope to agree with assessment by coronary angiography (fig 1). Where the slope agreed with the angiographic findings coronary artery narrowing may not have been the principal influence on myocardial ischaemia since scarring and cardiac enlargement could also have been influencing the results.

IMPLICATIONS

The above findings suggest that, in addition to being dependent on the severity of coronary artery disease, myocardial ischaemia early after myocardial infarction may be limited by scarring and may be increased by cardiac enlargement. This implies that in individual patients exercise induced myocardial ischaemia after recent myocardial infarction is determined by at least these three factors; however, the relative contribution of each is not known.

Cardiac enlargement in patients with myocardial infarction is also related to the degree of scarring,[13] and so differs from the enlargement seen with aortic valve disease. The present findings suggest that scarring may limit myocardial ischaemia attributable to coronary artery narrowing, and scarring also is likely to limit the influence of cardiac enlargement on the ischaemic process. This is evident from the group in which the slope underestimated the extent of coronary artery narrowing and who also had the largest left ventricular volumes (table). Animal studies have shown that a relative increase in left ventricular volume occurs even with small infarctions.[25] Where the effect of scarring is not great it should be possible to detect, using an index of myocardial ischaemia, the contribution of cardiac enlargement to the ischaemic process. This is supported by the findings from the patients in whom the slope overestimated the severity of coronary artery narrowing; this group had the best preserved left ventricular function.

Other possible explanations for the overestimation of coronary artery narrowing by the slope that was seen in some patients include drug treatment, distal coronary artery disease, and haematological abnormalities. An increase in the maximal ST/HR slope was seen when vasodilating drugs were used in patients with stable angina[15 16]; however, only two of the patients in the overestimate group were on such treatment. It is possible that distal coronary disease may be contributing to this "extra ischaemia"; trials of the use of the maximal ST/HR slope in patients with stable angina did not assess this aspect.[1] Abnormalities of platelet morphology have been reported in patients after acute myocardial infarction,[26] though further study is required to find out whether these changes contribute to ischaemia in the weeks after myocardial infarction.

The present findings may help to explain the reported discrepancy in the published reports regarding the value of exercise electrocardiography after infarction in detecting "multivessel disease".[27 28] Although the index of myocardial ischaemia used in such trials is open to criticism,[1] the discrepancy in results may also be due to influences other than coronary artery disease on myocardial ischaemia.

CONCLUSION

This study involving blind comparison of the maximal ST/HR slope with angiocardiography was aimed at testing the accuracy of the slope as an index of myocardial ischaemia early after myocardial infarction. The slope has been shown to be sensitive to the modifying influences of myocardial scarring and cardiac enlargement upon myocardial ischaemia soon after infarction. Exercise induced ischaemia early after myocardial infarction is influenced by myocardial scarring, cardiac enlargement, and significant narrowing of the coronary artery. Because ischaemia early after myocardial infarction is multifactorial, unlike ischaemia in patients with stable angina, the slope cannot be expected to detect the extent of significant coronary artery narrowing.

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References

1 Linden RJ, Mary DASG. Limitations and reliability of exercise electrocardiography tests in coronary heart disease. *Cardiovasc Res* 1982;**16**:675–710.

2 Mary DASG, Silverton NP, Boyle RM, Stoker JB, Smith DR, Linden RJ. The ST/HR slope as an index of ischaemic heart disease [Abstract]. *Circulation* 1985;**72** (suppl III):163.

3 Bishop N, Boyle R, Watson DA, Mary DASG, Linden RJ. The contribution of cardiac enlargement to myocardial ischaemia—assessment using the maximal ST/HR slope in patients before and after aortic valve surgery [Abstract]. *Clin Sci* 1985;**69** (suppl 12):55–6P.

4 Hoffman JIE. Why is myocardial ischaemia so commonly subendocardial? *Clin Sci* 1981;**61**:657–62.

5 Ellestad MH. *Stress testing. Principles and practice.* Philadelphia: Davis, 1981:321–3.

6 Castellanet MJ, Greenberg PS, Ellestad MH. Comparison of ST segment changes on exercise testing with angiographic findings in patients with prior myocardial infarction. *Am J Cardiol* 1978;**42**:29–35.

7 Cohn PF, Herman MV, Gorlin R. Profiles in coronary artery disease. In: Grossman W, ed. *Cardiac catheterization and angiography.* 2nd ed. Philadelphia. Lea and Febiger, 1980:325–35.

8 Baron MG. Radiological and angiographic examination of the heart. In: Braunwald E, ed. *Heart disease.* Philadelphia: WB Saunders, 1980:147–97.

9 Chen JTT. The chest roentgenogram. In: Hurst JW, ed. *The heart.* New York: McGraw Hill, 1982:278

10 Feigenbaum H. *Echocardiography.* 3rd ed. Philadelphia: Lea and Febiger, 1981:149–53.

11 Elamin MS, Boyle R, Kardash MM, *et al.* Accurate detection of coronary heart disease by new exercise test. *Br Heart J* 1982;**48**:311–20.

12 Elamin MS, Mary DASG, Smith DR, Linden RJ. Prediction of severity of coronary artery disease using slope of submaximal ST segment/heart rate relationship. *Cardiovasc Res* 1980;**14**:681–91.

13 Lamas GA, Pfeffer MA. Increased left ventricular volume following myocardial infarction in man. *Am Heart J* 1986;**111**:30–5.

14 Kennedy JW, Trenholme SE, Kasser IS Left ventric-

ular volume and mass from single plane cineangiocardiograms: a comparison of antero-posterior and right anterior oblique methods. *Am Heart J* 1970;**80**:343–52.

15 Bishop N, Hart G, Elamin MS, *et al.* Assessment of the effect of nifedipine on myocardial ischaemia by using the ST segment/heart rate slope. *Clin Sci* 1986; **70**:601–9.

16 Bishop N, Linden RJ, Mary DASG, Stoker JB. The effect of vasodilator drugs on myocardial ischaemia in stable angina using the maximal ST/HR slope [Abstract]. *Clin Sci* 1985;**70**(suppl 13):8P.

17 Quyyumi AA, Raphael MJ, Wright C, Bealing L, Fox KM. Inability of the ST segment/heart rate slope to predict accurately the severity of coronary artery disease. *Br Heart J* 1984;**51**:395–8.

18 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary angiographic findings. *Br Heart J* 1984;**52**:304–7.

19 Thwaites BC, Quyyumi AA, Raphael MJ, Canepa-Anson R, Fox KM. Comparison of the ST/heart rate slope with the modified Bruce exercise test in the detection of coronary artery disease. *Am J Cardiol* 1986;**57**:554–6.

20 Okin PM, Kligfield P, Ameisen O, Goldberg HL, Borer JS. Improved accuracy of the exercise electrocardiogram: identification of three-vessel coronary disease in stable angina pectoris by analysis of peak rate-related changes in ST segments. *Am J Cardiol* 1985;**55**:271–6.

21 Berenyi I, Hajduczki IS, Boszormenyi I. Quantitative evaluation of exercise-induced ST segment depression for estimation of degree of coronary artery disease *Eur Heart J* 1984;**5**:289–94

22 Finkelhor RS, Newhouse KE, Vrobel TR, Miron SD, Bahler RC. The ST segment/heart rate slope as a predictor of coronary artery disease: comparison with quantitative thallium imaging and conventional ST segment criteria. *Am Heart J* 1986;**112**:296–304.

23 Ameisen O, Okin PM, Devereux RB, *et al.* Predictive value and limitations of the ST/HR slope. *Br Heart J* 1985;**53**:547–51.

24 Rackley CE, Russell RO, Mantle JA, Rogers WJ, Papapietro SE. Modern approach to myocardial infarction: determination of prognosis and therapy. *Am Heart J* 1981;**101**:75–85.

25 Fletcher PJ, Pfeffer JM, Pfeffer MA, Braunwald E. Left ventricular diastolic pressure-volume relations in rats with healed myocardial infarction. *Circ Res* 1981;**49**:618–26

26 Martin JF, Plumb J, Kilbey RS, Kishk YT. Changes in volume and density of platelets in myocardial infarction. *Br Med J* 1983;**287**:456–8.

27 Akhras F, Upward J, Stott R, Jackson G. Early exercise testing and coronary angiography after uncomplicated myocardial infarction *Br Med J* 1982;**284**: 1293–4.

28 Peart I, Seth L, Albers C, Odemuyiwa O, Hall RJC. Post-infarction exercise testing in patients under 55 years: relation between ischaemic abnormalities and the extent of coronary artery disease. *Br Heart J* 1986;**55**:67–74.

Br Heart J 1987;57:521–7

The course of idiopathic dilated cardiomyopathy in New Zealand

HAMID IKRAM, HAMMOND G WILLIAMSON, MICHAEL WON,
IAN G CROZIER, ELIZABETH J WELLS

From the Departments of Cardiology and Community Medicine, The Princess Margaret Hospital, Christchurch, New Zealand

SUMMARY The course of dilated cardiomyopathy in New Zealand was studied in 72 cases that were followed up for $\leqslant 10$ years after cardiac catheterisation and coronary angiography. Eighty one per cent were male and 86% were white; the remainder were Maori. The mean age of patients at the time of investigation was 50·15 years. Most patients were unskilled labourers. The commonest presenting symptom was dyspnoea and the commonest physical sign was cardiomegaly. Mean survival time from first hospital presentation was 85 months; half the deaths were sudden. Factors predicting a poor survival included cardiomegaly, age, arrhythmias, cigarette smoking, and subclinical thiamine deficiency.

The syndrome of dilated cardiomyopathy in New Zealand appears to be identical with that seen in other European populations.

Dilated cardiomyopathy[1] causes considerable mortality and morbidity throughout the world. Despite extensive investigations the aetiology and course of this condition remain incompletely understood. The most likely aetiological factors are a genetic defect or some environmental factor causing progressive myocardial cell damage. Evidence for a genetic defect is slim in the usually sporadic cases of this condition, whereas several environmental factors are associated with dilated cardiomyopathy.[2] The most convincing evidence for an environmental aetiology comes from Keshan cardiomyopathy[3 4]—a form of dilated cardiomyopathy endemic to the Keshan region of China. This has been causally linked with a deficiency of selenium. Sporadic reports from the United States also implicate selenium deficiency in the aetiology of dilated cardiomyopathy in non-Chinese populations.[5 6] Links between the disease and other environmental factors are inconsistent.

There are few studies of the course of this disease. Most of these come from the United States or Europe. No long term studies have been done in New Zealand. For several reasons New Zealand is a natural experiment for the study of environmental influences in this disease. The population is mainly of Western European origin and New Zealand has the lowest soil content of selenium to which any European population is exposed. There is easy access to modern diagnosis and therapeutic facilities and the isolation of the country facilitates detailed long term follow up. A study of cardiomyopathy in such a setting may add to the understanding of this condition.

We report a 10 year prospective inquiry into the demographic, haemodynamic, and prognostic features of dilated cardiomyopathy as seen in New Zealand.

Patients and methods

PATIENTS

A prospective study of the course of dilated cardiomyopathy in New Zealand was started in 1974. All patients referred to one of us (HI) with cardiac failure of unknown aetiology were investigated by cardiac catheterisation and coronary angiography. Those in whom left ventricular ejection fraction was <50% and who did not have significant coronary artery disease (defined as 75% or greater cross sec-

Requests for reprints to Dr Hamid Ikram, Department of Cardiology, The Princess Margaret Hospital, Christchurch, New Zealand

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tional reduction of one or more major coronary vessels) were further investigated with a comprehensive protocol designed to establish aetiology of heart failure. Patients were excluded from the study if the investigations showed the presence of any agent known to cause cardiac muscle dysfunction—for example diabetes, hypertension, or collagen disorders. Those with rising titres of viral antibody were considered to have myocarditis and were also excluded. Patients exposed to certain factors suspected of being aetiological agents in dilated cardiomyopathy, such as excess consumption of alcohol and selenium deficiency, were included.

METHODS

Haemodynamic studies

Cardiac catheterisation was performed by the percutaneous technique through the femoral artery and vein. Right catheterisation was performed by means of a Swan-Ganz thermal dilution catheter which permitted measurement of pressure and cardiac output.

The left ventricle was catheterised with a pigtail catheter by the retrograde femoral approach. Cinefilms of left ventriculography were obtained in the 30° right anterior oblique projection after injection of 45 ml of Renografin. The ejection fraction was measured by means of digital callipers.[7]

Selective cineangiography of the coronary arteries was performed by the Judkins' technique; images were obtained in at least five planes for the left coronary artery and two for the right.

Left ventricular endomyocardial biopsy

Endomyocardial biopsy of the left ventricle was carried out by the long sheath technique.[8] A specially designed 8·5 French Teflon catheter with a haemostatic valve and side arm (Ikram sheath, Cook Inc, Australia) was inserted into the femoral artery over an 8 French pigtail catheter and advanced into the left ventricle. Multiple biopsy specimens were taken by means of a King's bioptome and fixed in glutaraldehyde for electron microscopy and formaldehyde for light microscopy. Morphometric analysis of the biopsy specimens was carried out as described elsewhere.[9]

Biochemical analyses

Concentrations of blood selenium were measured by the method of Watkinson.[10] Plasma transketolase concentrations were measured by the method of Warnock.[11]

Epidemiological methods

(*a*) Social class was defined according to occupational status; (*b*) alcohol excess was established by clinical assessment and by response to the Canterbury alcoholism screening test[12]; (*c*) cigarette smoking was measured as pack years—that is the number of packets of 20 cigarettes smoked per day multiplied by the number of years the subject had smoked; (*d*) survival was calculated from the first hospital admission for cardiac disease (follow up details were obtained by outpatient evaluation in surviving patients and from relatives, family doctors, and the Registry of Births and Deaths for those who had died); (*e*) sudden death was defined as death occurring within 24 hours without previous symptoms.

Statistical methods

Standard descriptive statistical variables such as the means, standard deviations, and standard errors were calculated by standard formulas and a BMDP program.[13] The influence of selected clinical, haemodynamic, and biochemical variables on survival was examined by the life table method with program PII of the BMDP statistical package. The generalised Wilcoxon[14] and the generalised Savage[15] tests were used to evaluate the significance of a particular variable on survival. The Wilcoxon test is more sensitive to short term effects, whereas the Savage test is more suitable for long term trends.

Results

Only four patients were lost to follow up. They were counted as being alive up to their last follow up visit.

DEMOGRAPHIC FEATURES

Incidence

Since 1975 there have been 72 cases of dilated cardiomyopathy in a population of 350 000. This gives an annual incidence of 2·0/100 100 population. This is almost certainly an underestimate because some cases will have been referred to other physicians. The case incidence remained fairly constant at six per annum except for 1977 when there was a threefold increase.

Age, sex, and race

The ages at time of catheterisation ranged from 22 to 74 years with a mean (SD) of 50·15 (10·64) years. Eighty one per cent of the patients were men and 86% were white; the remainder were Maori. The number of Maoris was disproportionally high because only 2% of the total referral population were Maoris.

Social and educational status

The majority of the study population were unskilled labourers but there were very few unemployed people (table 1). Executive, managerial, and professional classes were conspicuously absent and only one person had a university degree.

CLINICAL FEATURES

Presenting symptoms

The commonest presenting symptom at the first cardiac admission was dyspnoea. Table 2 shows the other major symptoms.

Physical examination

The commonest physical finding was cardiomegaly. Table 2 lists the frequency of other physical findings.

Electrocardiographic findings

Only 7% of patients presented with an entirely normal electrocardiogram. The most frequent findings were non-specific repolarisation changes.

Radiological findings

The cardiothoracic ratio was increased in all the patients at the time of catheterisation. The degree of cardiomegaly was the strongest predictor of both long and short term prognosis.

HAEMODYNAMIC DATA

Of the many haemodynamic variables that were assessed only the pulmonary arterial pressure correlated significantly with prognosis. The left ventricular ejection fraction was one notable index that did not predict survival.

MODE OF DEATH

Half of the patients died suddenly. In 67% death occurred out of hospital. Of those not dying suddenly, 67% died of progressive cardiac failure and two died of massive pulmonary emboli. Non-cardiac deaths were due to accident in two and suicide in one. The cause of death could not be established in six cases.

Table 1 *Social and educational data on 72 patients with catheter diagnosed idiopathic dilated cardiomyopathy in New Zealand*

Social and educational status	*Total*
White collar	2
Blue collar	22
Unskilled labourer	27
Housewife	9
Student	1
Alcohol related	3
Retired	5
Unemployed	2
Chronic sickness benefit	1

Table 2 *Symptoms and signs at presentation of 72 patients with idiopathic dilated cardiomyopathy*

	Total (%)
Symptoms:	
Dyspnoea	61 (85)
Chest pain	26 (36)
Palpitation	34 (47)
Fainting	6 (8)
Embolic	4 (6)
Signs:	
Clinical cardiomegaly	46 (64)
Ascites	36 (50)
Raised jugular venous pressure	37 (51)
Oedema	23 (32)
Third heart sound	23 (32)
Hepatomegaly	17 (24)
Rales	17 (24)

SURVIVAL DATA

Figure 1 shows our results and the results of two studies from the United States[16 17] and one from Germany[18] that had similar inclusion criteria. The mean survival time for our series was 85 months. This is similar to that in two other studies.[16 18] The study of Fuster *et al* has a slope identical with that in the other two studies but a different intercept, suggesting that the patients had more advanced disease but that their attrition rate was similar to ours.[17] Table 3 lists the factors influencing survival.

Discussion

Though the term idiopathic dilated cardiomyopathy is a convenient description for a syndrome resulting from cardiac muscle dysfunction it does not describe a homogenous entity. Even this broad definition is a misnomer because the same cardiac dysfunction can occur in the absence of dilatation[19] or be confined to one ventricle.[20] With growth of knowledge and

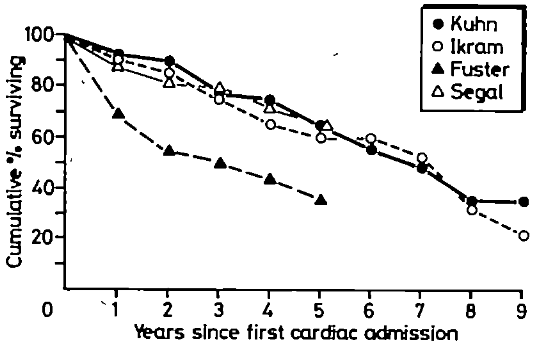

Fig 1 *Cumulative survival from first cardiac admission in the present series of dilated cardiomyopathy and in three others with similar entry criteria.*

Table 3 *Statistical significance of adverse prognostic factors in dilated cardiomyopathy*

Factor	*Wilcoxon*	*Savage*
Cardiothoracic ratio	p < 0·0075	p < 0·009
Sinus tachycardia	p < 0·0320	p < 0·0134
Increasing age	p < 0·0457	p < 0·0224
Rhythm other than sinus	p < 0·0433	p < 0·0675
Increasing pulmonary artery systolic pressure	p < 0·0795	p < 0·0250
Increasing cigarette consumption	p < 0·1103	p < 0·0541
Abnormal transketolase concentration	p < 0·1620	p < 0·0505

techniques, specific aetiological agents will be identified and reclassified as distinct disorders.

Our study shows that the incidence of dilated cardiomyopathy in New Zealand is similar to that in other developed countries.[21] The various risk factors resemble those noted in other countries. The preponderance of men[16 17 22] and those in the lower socioeconomic classes[23 24] has been reported by others. Of other factors thought to be of aetiological importance, alcohol is the most commonly reported. Some authorities consider that alcoholic cardiomyopathy is a specific entity which should not be classified as idiopathic dilated cardiomyopathy. Alexander reported a series of 100 patients with cardiomyopathy, 83 of whom were judged to be alcoholics.[25] His definition of excess alcohol consumption was at least four pints of beer or two measures of whisky a day. By these criteria 28% of his non-cardiomyopathic hospital admissions were alcoholics. Brigden and Robinson, on the other hand, defined alcoholism as a daily intake of 15 pints of beer or a 750 ml bottle of spirits.[26] This variation illustrates some of the problems in attempting to define the role of alcohol in this disorder. Furthermore, unexceptional quantities of alcohol may be associated with cardiomyopathy in some individuals but not in others. Virtually all workers are agreed that it is exceptional to have evidence of other alcohol related disease in these patients. Diagnosis is complicated by the great difficulty in obtaining a reliable estimate of alcohol intake in alcoholics or even establishing whether the patient is drinking or not. Alcohol abuse also rarely occurs in isolation—it is often associated with cigarette smoking and faulty nutrition. Some series have reported improved survival in patients who became abstinent[27]; however, others have not.[28] In our series about 50% of the patients were believed to be alcoholic, which is a lower percentage than some studies.[26 27] The survival curves for alcoholics and non-alcoholics were identical, however (fig 2). This casts doubt on the primary aetiological role of alcohol.

The increased frequency of dilated cardiomyopathy in low socioeconomic classes, poorer countries, and in alcoholics has led to the suggestion that it may be related to faulty nutrition rather than a direct effect of alcohol. The nutritional factor most investigated has been thiamine. Cardiac beriberi is a distinct clinical entity and not readily confused with dilated cardiomyopathy. It was present in 20% of Alexander's cases[25] and in 9·5% of our entire cardiomyopathic series. In the present study, however, we noted that a mildly abnormal transketolase test, which is not diagnostic of beriberi, was not rare and that it significantly predicted survival. Since this test indicates thiamine deficiency it suggests that subclinical deficiency of thiamine is frequent and does influence survival and may be aetiologically important. The validity of this observation can only be proved by a controlled trial of thiamine administration, but the present data are highly suggestive of such a relation.

Recent studies on animal models[29 30] and patients[31] suggest that smoking may have an aetiological role in dilated cardiomyopathy even in the absence of coronary vascular disease. About 35% of our series of patients were cigarette smokers; this is no more than in the general population. In the absence of a control group we cannot assess the aetiological importance of cigarette smoking. The survival data do show a worse prognosis with increasing cigarette smoking. The reasons for this remain speculative but they may relate to the increased risk of sudden death in smokers.[32] Since half our patients died suddenly, smoking may be an important prognostic factor.

Selenium deficiency was first described as a cause of myopathy (including cardiomyopathy) in New Zealand lambs.[33 34] Our referral population comes from an area which has one of the lowest soil selenium contents in the country. The human equivalent of this animal cardiomyopathy is Keshan dis-

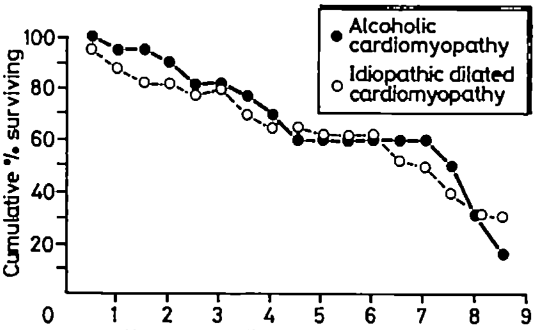

Fig 2 *Comparative cumulative survival from first cardiac admission for idiopathic cardiomyopathy (51 cases) and alcoholic cardiomyopathy (21 cases)*

ease, a dilated cardiomyopathy endemic to the Keshan region of China where the soil is very deficient in selenium. If selenium deficiency is an aetiological factor in dilated cardiomyopathy in New Zealand an incidence of epidemic proportions would be expected; this is not the case. In Keshan, however, the mean concentration of blood selenium in affected individuals was 20 μg/ml whereas unaffected residents had a mean concentration of about 40 μg/ml. (J Watkinson, 1985, personal communication.) The mean concentration in our cardiomyopathy patients was 57 8 μg/ml, which although it is lower than the concentration in healthy blood donors from our area (42 to 190 μg/ml) and the United States (100 to 340 μg/ml), is not as low as in Keshan patients. The reason for the lack of selenium related cardiomyopathy in New Zealand may simply be that the concentrations of the trace metal are not low enough to cause the disease in man, who may be less susceptible than animals. Alternatively, selenium deficiency may be only one of the factors responsible. Not all Chinese experts agree that selenium deficiency is the most important factor in the aetiology of Keshan cardiomyopathy.[35] Without a controlled trial of selenium supplements we cannot be certain about the aetiological importance of selenium deficiency; however, we found that once the condition is clinically obvious the concentration of blood selenium had no bearing on prognosis.

Our data indicate that the prevalence of various proposed aetiological agents of idiopathic dilated cardiomyopathy is the same in New Zealand as elsewhere. This suggests that the cause or causes of this condition lie in common factors that are universally present.

The course of dilated cardiomyopathy in Australasia is largely unknown. This study suggests that the prognosis is relatively good. The mean survival of 85 months is significantly better than the study reported from the Mayo Clinic in which 75% of patients died within the first two years.[17] It is also better than the survival of patients with coronary artery disease and a history of heart failure; these patients had a mean survival of four years irrespective of their New York Heart Association functional class.[36] Franciosa *et al* also reported a better prognosis in dilated cardiomyopathy than in coronary disease.[37] Reports from many countries report a long survival in patients with dilated cardiomyopathy. Kuhn from West Germany,[18] Segal *et al* from the United States[16] and Hatle from Norway,[38] who all date their survival from the first definite cardiac symptoms, report a survival experience similar to ours. Even the series from the Mayo Clinic[17] in which a very poor survival rate was reported shows an identical slope to our study and the other studies—only the intercept is different. This suggests that the attrition rate in all these series is the same; the different intercept indicates that the series with shorter survival had included patients with more advanced disease. A similar difference in prognosis between major teaching hospitals and district hospitals has been reported for hypertrophic cardiomyopathy.[39]

Survival was unrelated to sex or to race. Increasing age was associated with a poorer prognosis. This observation was also made by others[17 23] but denied by some.[40] Cardiac size on the chest radiograph emerged as the best predictor of prognosis in this series as in several others.[16 17] The adverse prognostic significance of atrial fibrillation[16] was also confirmed. The predictive value of haemodynamic measurements was disappointing, particularly that of the left ventricular ejection fraction. This is a much debated point; some find it of great value[40] while others do not.[23] The same is true of myocardial histology. Like others we did not find that the results of myocardial biopsy added further prognostic information,[22] but there are reports that histological changes are independent predictors of survival.[18 41]

These patients die either of progressive cardiac failure or of sudden unexpected death presumably caused by an arrhythmia. There is disagreement about the proportions of deaths caused by these two mechanisms. Our findings were similar to those of Johnson and Palacios who reported a 45% frequency of sudden death in their series.[23] Segal *et al* reported a 29% frequency of sudden death,[16] but they also reported that an additional 10% of their deaths were caused by arrhythmias. Sudden death is undoubtedly common in these patients.

The course of the disease followed three patterns. The first was inexorable decline with death in one to two years. The second was deterioration followed by stabilisation and even temporary improvement in some, followed by further decline, the whole course being long drawn out (> 15 years). We have, however, never seen complete recovery in a patient with established cardiomyopathy. The third pattern of natural progress is a variable, often slow, decline ending in sudden unexpected death. This latter course, which often occurs in patients with haemodynamically mild disease, may prevent a close relation between haemodynamic variables and prognosis.

It is difficult to judge the influence of treatment on survival in an uncontrolled study such as this. The only class of drugs that may improve prognosis in heart failure are the angiotensin converting enzyme inhibitors[42] and even for these the evidence is slim. We compared the survival in our patients before

1980, when these drugs first became available to us, with survival after this time. We were unable to show any significant differences; however, the numbers were small.

This study shows that the clinical syndrome of dilated cardiomyopathy has virtually the same incidence, aetiology, and course in New Zealand residents as in other European populations. It suggests that some commonly encountered factor or factors are responsible for this disorder.

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References

1 Report of the WHO/IFSC task force on the definition and classification of cardiomyopathies. *Br Heart J* 1980;44:672–3.

2 Goodwin JF. Introduction, problems and aims of the Multicentre Research Project. *Postgrad Med J* 1978;54:431–2.

3 Keshan Disease Research Group. Epidemiologic studies on the etiologic relationship of selenium and Keshan disease. *Chin Med J [Engl]* 1979;92:477–82.

4 Keshan Disease Research Group. Observations on the effect of sodium selenite in the prevention of Keshan disease. *Chin Med J [Engl]* 1979;92.471–7.

5 Johnson RA, Baker SS, Fallon JT. An occidental case of cardiomyopathy and selenium deficiency. *N Engl J Med* 1981;304.1210–2

6 Collipp PJ, Chen SY. Cardiomyopathy and selenium deficiency in a 2 year old girl. *N Engl J Med* 1981; 304:1304–5.

7 Bones PJ, Ikram H. A method of left ventricular function estimation from cine-angiograms employing a special purpose calculator. *Cardiovasc Res* 1977; 11:470–4

8 Brooksby IAB, Jenkins BS, Coltart DJ, Webb-Peploe MM. Left ventricular endomyocardial biopsy. *Lancet* 1974;ii:1222–5.

9 Ikram H, Maslowski AH, Smith BL, Nicholls MG. The hemodynamic histopathological and hormonal features of alcoholic cardiac beri-beri. *Q J Med* 1981;50:359–75.

10 Watkinson JH. Fluorimetric determination of traces of selenium. *Anal Chem* 1960;32:981–3.

11 Warnock LG. The measurement of erythrocyte thiamine pyrophosphate by high performance liquid chromatography. *Anal Biochem* 1982;126:394–7.

12 Elvy GA, Wells JE. The Canterbury alcoholism screening test (CAST): a detection instrument for the use with hospitalised patients. *NZ Med J* 1984;97:111–5.

13 Dixon WJ. *BMDP statistical software* Berkeley· University of California, 1981.

14 Breslow N. A generalised Kruskal-Wallis test for comparing K samples subject to unequal patterns of censorship. *Biometrika* 1970;57:579–94.

15 Mantel N. Evaluation of survival data and two new rank order statistics arising in this consideration. *Cancer Chem Rep* 1966;50:163–70

16 Segal JP, Stapleton JF, McClellan JR, Waller BF, Harvey WP. Idiopathic cardiomyopathy. clinical features, prognosis and therapy. *Curr Probl Cardiol* 1978;3:9–49.

17 Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of dilated cardiomyopathy. *Am J Cardiol* 1981;47:525–31.

18 Kuhn H, Breithardt G, Knieriem HJ, *et al.* Prognosis and possible presymptomatic manifestations of congestive cardiomyopathy. *Postgrad Med J* 1978;54: 451–9.

19 Keren A, Billingham ME, Weintraub D, Stinson EB, Popp RL. Mildly dilated congestive cardiomyopathy. *Circulation* 1985;72:302–4.

20 Fitchett DH, Sugrue DD, MacArthur CG, Oakley CM. Right ventricular dilated cardiomyopathy. *Br Heart J* 1984;51·25–9.

21 Torp A. Incidence of congestive cardiomyopathy. *Postgrad Med J* 1978;54:435–7.

22 Schwarz F, Mall G, Zebe H, *et al.* Determinants of survival in patients with congestive cardiomyopathy: quantitative morphologic findings and left ventricular hemodynamics. *Circulation* 1984;70:923–8.

23 Johnson RA, Palacios I. Dilated cardiomyopathies of the adult. Part 1. *N Engl J Med* 1982;307:1051–8.

24 Hill KR, Still WJS, McKinney B. Jamaican cardiomyopathy. *Br Heart J* 1967;29:594–601.

25 Alexander CS. Idiopathic heart disease 1. Analysis of 100 cases with special reference to chronic alcoholism. *Am J Med* 1966,41:213–28.

26 Brigden WW, Robinson JF. Alcoholic heart disease *Br Med J* 1964;ii:1283–9.

27 Demakis JG, Proskey A, Rahimtoola SH, *et al.* The natural course of alcoholic cardiomyopathy. *Ann Intern Med* 1974;80:293–7.

28 Shugoll GI, Bowen PJ, Moore JP, Lenkin ML. Follow up observations and prognosis in primary myocardial diseases. *Arch Intern Med* 1972,129:67–72.

29 Kjeldsen K, Thomsen HK, Astrup P. Effects of carbon monoxide on myocardium. Ultrastructural changes in rabbits after moderate chronic exposure. *Circ Res* 1974;34:339–48.

30 Gvozdjkova A, Bada V, Sany L, *et al* Smoke cardiomyopathy: disturbance of oxidative processes in myocardial mitochondria. *Cardiovasc Res* 1984;18: 229–32.

31 Hartz AJ, Anderson AJ, Brooks HL, Manley JC, Parent GT, Barboriak JJ. The association of smoking with cardiomyopathy. *N Engl J Med* 1984;311: 1201–6.

32 Hallstrom AP, Cobb LA, Ray R Smoking as a risk

Parent GT, Barboriak JJ. The association of smoking with cardiomyopathy. *N Engl J Med* 1984;**311** 1201–6.

32 Hallstrom AP, Cobb LA, Ray R. Smoking as a risk factor for recurrence of sudden cardiac arrest. *N Engl J Med* 1986;**314**:271–5.

33 Hartley WJ. "Stiff-lamb disease" in New Zealand. *NZ Vet J* 1953;**1**:137–42.

34 Robertson TG, During C. Lamb dosing trials with selenium and cobalt *NZ J Agric* 1961;**103**:306–10.

35 Guanqing H. On the etiology of Keshan disease. Two hypotheses. *Chin Med J [Engl]* 1979;**92**:416–22.

36 Califf RM, Bounous P, Harrell FE, *et al*. The prognosis of heart failure in the presence of coronary artery disease In: Braunwald E, Mock MB, Watson J, eds. *Congestive heart failure. Current research and clinical applications.* New York: Grune and Stratton, 1982:31–40.

37 Franciosa JA, Wilen M, Ziesche S, Cohn JN. Survival

38 Hatle L, Orjavik O, Storstein O. Chronic myocardial disease. 1. Clinical picture related to long term prognosis. *Acta Med Scand* 1976;**199**·399–405

39 Shapiro LM, Zezulka A. Hypertrophic cardiomyopathy: a common disease with a good prognosis. Five year experience of a district general hospital. *Br Heart J* 1983;**50**:530–3.

40 Unverferth DV, Magorien RD, Moeschberger ML, Baker PB, Fetters JK, Leier CV. Factors influencing the one-year mortality of dilated cardiomyopathy *Am J Cardiol* 1984;**54**.147–52.

41 Figulla HR, Rahlf G, Neiger M, Luig H, Kreuzer H Spontaneous hemodynamic improvement or stabilization and association biopsy findings in patients with congestive cardiomyopathy. *Circulation* 1985; **71**:1095–104.

42 Furberg CD, Yusuf S. Effects of vasodilators on survival in chronic congestive heart failure. *Am J Cardiol* 1985;**55**:1110–3.

Br Heart J 1987;57:528–33

Doppler echocardiographic evaluation of the normal human fetal heart

LINDSEY D ALLAN, SUNDER K CHITA, WIDAD AL-GHAZALI,
DIANE C CRAWFORD, MICHAEL TYNAN

From the Departments of Perinatal and Paediatric Cardiology, Guy's Hospital, London

SUMMARY Pulsed wave Doppler estimates of blood flow velocity were made across the mitral, tricuspid, aortic, and pulmonary valves in a series of 120 normal fetuses (gestational age 16–36 weeks). In 36 of these the data were obtained in all four sites. The maximum and mean velocities were calculated for each valve and these values were plotted against gestational age. There was little change in these values throughout pregnancy. The orifice dimensions of the valves were measured by cross sectional echocardiography. At all ages the tricuspid orifice was larger than the mitral and the pulmonary orifice was larger than the aortic. The blood flow values for each valve were derived from the product of the mean velocity and the valve orifice dimensions. The output of the right ventricle was usually, but not always, greater than that of the left ventricle. Combined ventricular output increased from approximately 50 ml/min at 18 weeks to 1200 ml/min at term.

Despite limitations in the accuracy of the technique these results form a useful basis for the analysis of blood flow in the normal fetus and for the interpretation of abnormal Doppler findings in prenatal life.

The anatomy of the fetal heart can be readily examined by echocardiography from as early as 16 weeks' gestation.[1] Both normal and abnormal structure can be identified.[2 3] Blood flow velocity can now be estimated by Doppler examination in conjunction with cross sectional imaging. The volume of blood flow across each cardiac valve can be derived from the Doppler study.[4 5] Previous work on fetal haemodynamic function has centred mainly on the lamb; in this study we report the Doppler evaluation of blood flow in a series of normal human fetuses.

Patients and methods

Patients were selected at random from pregnant women attending for fetal echocardiography because of a family history of congenital heart disease or attending the antenatal clinic. An initial fetal echocardiogram was performed to ensure that the fetal heart was structurally normal. Patients with any abnormality of pregnancy were excluded from the study. All pregnancies were dated by early estimation of the biparietal diameter or the femoral length or both.

A Hewlett Packard 77020A phased array sector scanner was used with a 5 MHz transducer. Occasionally, in late pregnancy adequate imaging could only be obtained with a 3 MHz transducer. In order to minimise errors in measurement only subjects in whom good quality images were achieved were included in the study. The total ultrasound examination time was limited to 30 minutes per patient. Within this time constraint it was not possible to obtain Doppler velocity traces of optimal quality at all four sites in every patient. Poor quality traces were excluded from analysis. Thus the patients were not consecutive.

Doppler velocity measurements were obtained by placing the sample volume just distal to the atrioventricular valve leaflets in the left or right ventricles and distal to the arterial valve in the aorta or the pulmonary artery. Only an angle of <20° between the direction of flow and the direction of the Doppler beam was regarded as acceptable. With our equipment the angle is indicated manually by the

Requests for reprints to Dr Lindsey D Allan, Department of Perinatal Cardiology, Guy's Hospital, St Thomas Street, London SE1 9RT.

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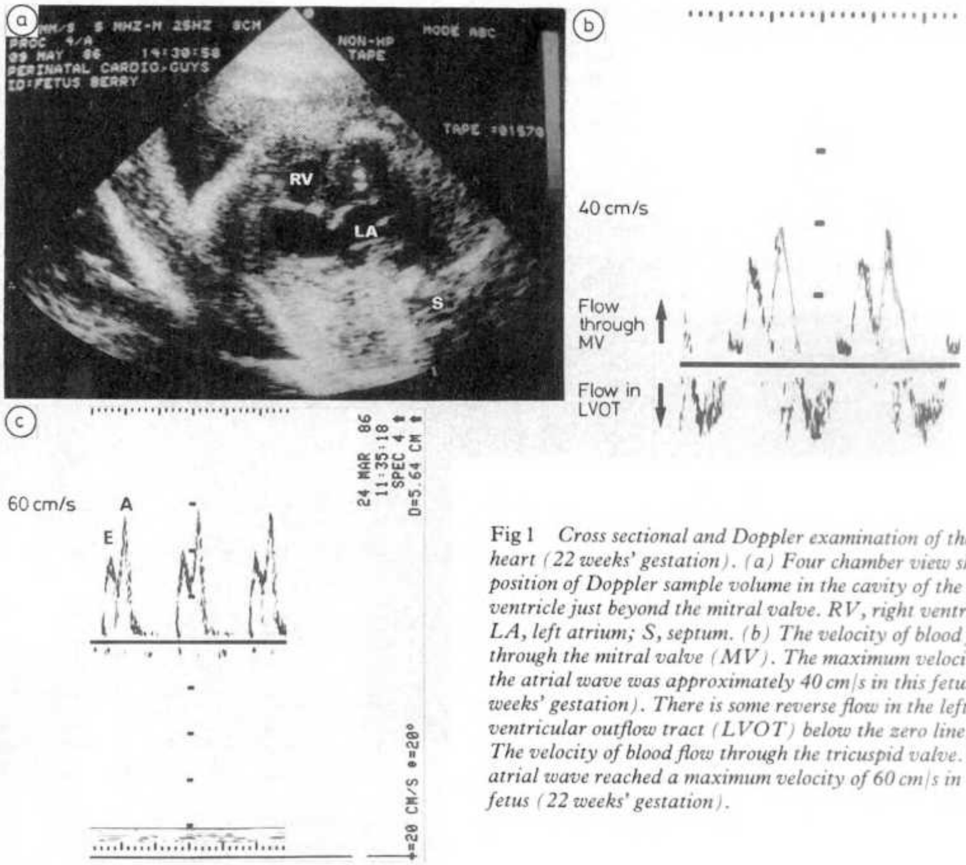

Fig 1 *Cross sectional and Doppler examination of the fetal heart (22 weeks' gestation). (a) Four chamber view showing position of Doppler sample volume in the cavity of the left ventricle just beyond the mitral valve. RV, right ventricle; LA, left atrium; S, septum. (b) The velocity of blood flow through the mitral valve (MV). The maximum velocity of the atrial wave was approximately 40 cm/s in this fetus (22 weeks' gestation). There is some reverse flow in the left ventricular outflow tract (LVOT) below the zero line. (c) The velocity of blood flow through the tricuspid valve. The atrial wave reached a maximum velocity of 60 cm/s in this fetus (22 weeks' gestation).*

operator and is automatically corrected in the velocity display. The orifice was measured with callipers on the frozen frame image of the valve under examination. The mitral and tricuspid orifices were measured in diastole in the apical four chamber view. The internal diameter of the aorta and the pulmonary artery were measured, also in diastole, at the tip of the closed arterial valve. For these measurements the origin of the great artery was viewed in the long axis, the ultrasound beam being directed perpendicularly to the walls of the artery whenever possible. All valve orifices were assumed to be circular for the calculation of their cross sectional area.

The maximum velocity through each valve was estimated from the paper recording of the velocity trace. Traces with variations in velocity caused by fetal breathing or other fetal movement were not used for analysis. In acceptable traces the mean temporal velocity was calculated by planimetry of the area under the spectral velocity record throughout the cardiac cycle; this was then divided by the time over which the flow was traced. Flow velocities were traced along the zero line during diastole for the arterial valves and during systole for the atrioventricular valves. Figure 1a shows a four chamber view suitable for atrioventricular valve interrogation. The Doppler sample volume was positioned just beyond the mitral valve orifice, and fig 1b shows a representative trace achieved in this position. In early pregnancy the sample overlapped the outflow tract of the left ventricle, hence reverse flow was seen during diastole in this tracing. This was of no importance because it was not included in the flow calculation. This effect was minimised by placing the sample volume as close as possible to the wall of the left ventricle. Figure 1c shows a tracing of tricuspid valve flow velocity. This shows the double peaked velocity trace through both atrioventricular valves. The first peak is the passive filling phase and the second is associated with atrial systole.

Figure 2 shows the sample volume suitably positioned in the pulmonary artery (a) with the resulting velocity trace (b). Figure 3a shows the position of the sample volume in the aorta and fig 3b the velocity recorded in this site. The arterial trace showed one velocity peak with a similar acceleration and time to peak velocity in both the aorta and the pulmonary artery.

For measurements in all sites the mean of three consecutive cardiac cycles was used for the flow calculation. Volume flow was calculated for each valve from the formula:

$$Q = \text{mean (angle corrected) velocity} \times \text{valve area.}$$

Results are expressed as mean (2 SD). Linear correlation was performed to compare mitral with aortic flow and tricuspid with pulmonary flow. Similar methods were used to relate velocity to gestational age. We used multiple regression to examine various models expressing the relation between the diameter or flow and the gestational age with or without variation between the mitral and tricuspid valves. The simplest equations which fitted adequately are given. This was repeated for the aortic and pulmonary valves. The null hypothesis was retained when $p > 0{\cdot}05$.

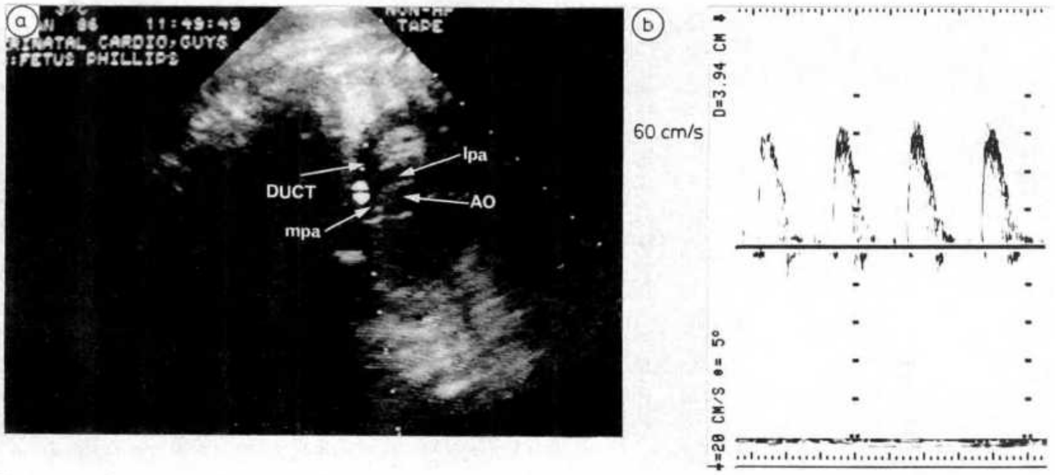

Fig 2 *(a) Cross sectional view showing position of the Doppler sample volume in the pulmonary artery. The angle of insonation is very close to the line of blood flow. (b) Pulmonary artery velocity tracing at 24 weeks' gestation. The maximum velocity is approximately 65 cm/s in this recording. DUCT, ductus arteriosus; AO, aorta; lpa, left pulmonary artery; mpa, main pulmonary artery.*

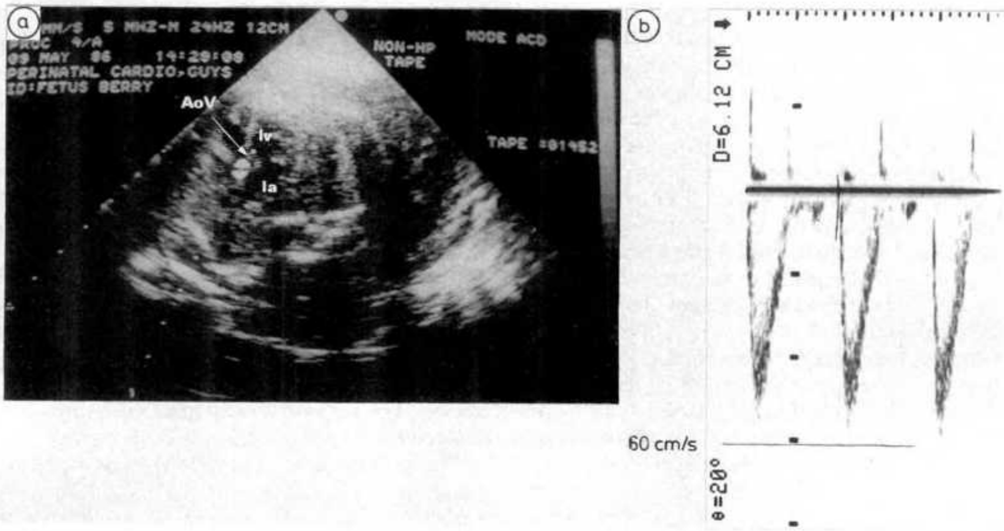

Fig 3 *(a) Cross sectional apical view showing position of the Doppler sample volume in the ascending aorta. Imaging from the left ventricular apex gives a good angle of insonation. lv, left ventricle; la, left atrium; AoV, aortic valve. (b) The maximum velocity of aortic blood reached 55 cm/s in this fetus (22 weeks' gestation).*

Results

Adequate images and Doppler traces were obtained in all four sites in 36 fetuses. In the remaining 84 data were obtained from only two or three sites.

The maximum velocity of flow through the atrioventricular valves did not change throughout pregnancy. It remained at a mean of 51·65 (19·4) cm/s through the tricuspid valve and at a mean of 48·49 (20·8) cm/s through the mitral valve. The mean velocity of flow through the tricuspid valve was 13·5 (6) cm/s while that through the mitral was 12·5 (5·2) cm/s. Like the maximum velocity, the mean velocity did not change significantly during pregnancy. The differences between the tricuspid and mitral valve values for maximum and mean velocities were not statistically significant. The atrioventricular and arterial valve diameters increased as the heart grew; fig 4 shows the mean values for their dimensions. There was a linear relation between all four valves and gestational age. The relevant lines for the atrioventricular values shown in fig 4 have a constant intercept but significantly different slopes (p < 0·001). The fit was not significantly better if the intercepts were varied. The same is true of the arterial valves, the pulmonary artery being significantly larger than the aorta (p < 0·001).

The maximum velocity in both great arteries ranged from 30 cm/s at 16 weeks' gestation to 100 cm/s at term. The mean velocity of aortic flow was a mean of 18 (8·6) cm/s and that in the pulmonary artery was 17·2 (8) cm/s. Mean velocity in the great arteries appeared to increase as pregnancy advanced but this increase was not statistically significant, nor was the difference between the mean velocity in the two great arteries.

Figure 5 shows the calculated volume flows (ml/min) for each atrioventricular valve and for the arterial valves. The increase in volume flow with increasing gestational age is accounted for by the increase in the size of the valve orifices. The relations between mitral and tricuspid valve flows and gestational age were linear after log transformation, and lines of constant slope but significantly different intercepts (p < 0·001) were fitted. The fit was not significantly better if different slopes were fitted to results from the two valves. Figure 5 shows the relation between flow and ges-

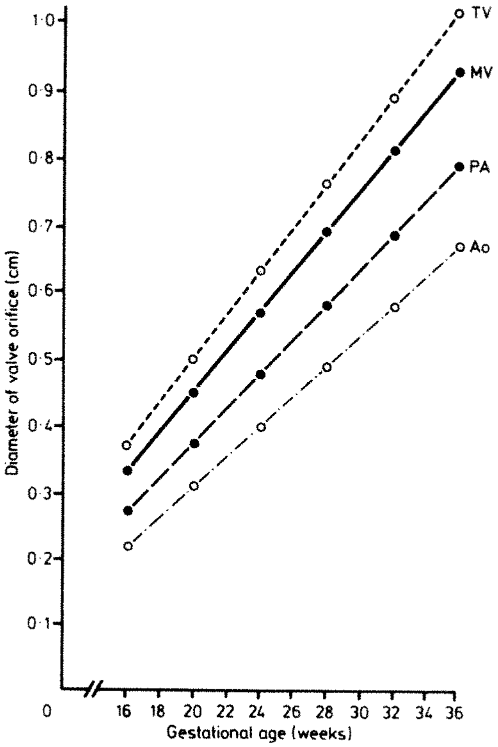

Fig 4 *The diameters of all four valves increased throughout pregnancy. At all times the tricuspid (TV) was slightly larger than the mitral (MV) orifice and the pulmonary (PA) orifice was larger than the aortic (Ao) orifice. MV = −0·146 + 0·0300 gestational age; TV = −0·146 + 0·0324 gestational age; Ao = −0·138 + 0·0224 gestational age; PA = −0·138 + 0·0257 gestational age.*

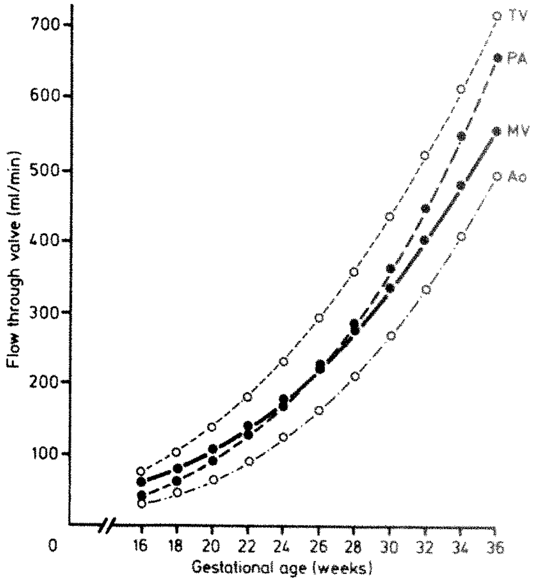

Fig 5 *Valve flow increased throughout pregnancy. Between 32 and 34 weeks' gestation the combined ventricular output totalled approximately 1 l/min. TV flow = 0·03585 (gestation)*$^{2\cdot76}$*; MV flow = 0·02787 (gestation)*$^{2\cdot76}$*; Ao flow = 0·003139 (gestation)*$^{3\cdot34}$*; PA flow = 0·004201 (gestation)*$^{3\cdot34}$*. See legend to fig 4 for abbreviations.*

tational age for both these valves on transforming back. A similar transformation was required for the aortic and pulmonary valve flows and the best fit was achieved with two lines of constant slope but significantly different intercepts ($p \leqslant 0{\cdot}001$). Again fig 5 shows the relationships on transforming back.

To test the validity of the flow calculations, linear correlations between the mitral and the aortic and the tricuspid and the pulmonary flows were calculated for the 36 fetuses with measurements in all four sites (figs 6 and 7). The data from these 36 fetuses gives information on the relative outputs of the right and left ventricles. When this was estimated from the atrioventricular valve flow the right ventricular output exceeded that of the left ventricle according to the regression equation:

tricuspid flow = 12·56 + 1·32 × mitral flow;

the ratio of tricuspid to mitral flow ranged from 0·8 to 2·2 (mean 1·3). Similarly, pulmonary artery flow exceeded aortic flow. The regression equation was:

pulmonary artery flow = 49·25 + 1·05 × aortic flow;

the ratio of pulmonary artery to aortic flow ranged from 0·8 to 2·5 (mean 1·4).

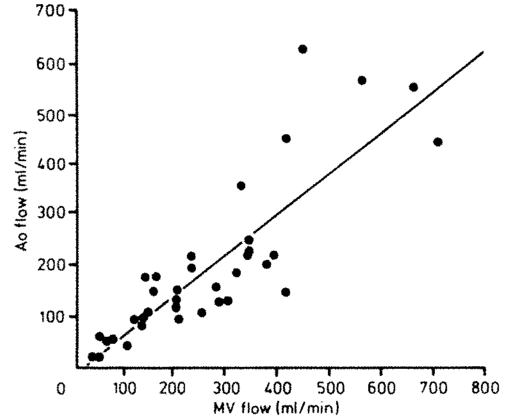

Fig 6 *Comparison of estimated aortic (Ao) and mitral valve (MV) blood flows in the same 36 fetuses. The derived regression equation is aortic flow = −10·2 + 0·82 × mitral flow, with r = 0·874.*

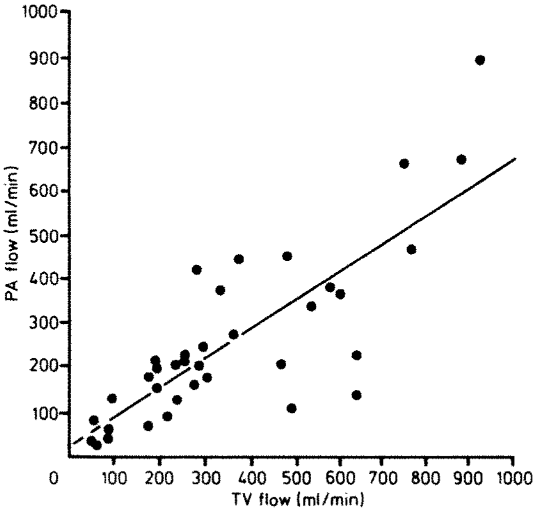

Fig 7 *Comparison of pulmonary (PA) and tricuspid valve (TV) blood flows in the same 36 fetuses. The regression equation is pulmonary flow = 21·27 + 0·68 × tricuspid flow, with r = 0·82.*

Discussion

The good correlation between atrioventricular valve flow and flow in the corresponding great artery corroborates the validity of Doppler derived volume flow estimates in the human fetus. This is important since, of necessity, the experimental study of the fetal circulation has hitherto been confined to animals. Although the same principles of cardiovascular physiology apply to man and the lamb it is unwise to extrapolate directly from one species to another. The techniques described in this report allow us to gain direct and detailed insights into the cardiovascular performance of the normal intact human fetus.

The measurement of maximum velocity is accurate and reproducible and knowledge of the normal values in the fetus is important when such measurements are made in the presence of structural cardiac abnormality. For example, valve stenosis in prenatal life, as in postnatal life, will increase the maximum velocity across the affected valve.

Although the velocity measurements are accurate, the derived volume flow estimates are subject to error in the measurement and calculation of valve orifice area. The scatter of dimension measurements was greater for the atrioventricular than for the arterial valves. In our experience the decision about which dimension to take as the diameter to measure at the atrioventricular valve is more subjective than the decision at arterial valve. Any error is magnified when the radius is squared in the volume flow calculation. A further possible source of error is the assumption that all four valves are circular in cross section. This is probably true for the arterial valves but may not accurately reflect the geometry of the atrioventricular orifices. For these reasons, and because it is easier, we prefer to take the estimate of flow obtained in the great arteries as the output of that ventricle. Despite these reservations the correlation between atrioventricular valves and arterial valve flows is, as stated above, good.

Examination of fig 5 shows that the combined ventricular output at 26 weeks' gestation is approximately 450 ml/min, slightly more if atrioventricular valve flow is used and slightly less if arterial valve flow is used. At this gestational age the fetal body weight is approximately 1 kg. Thus the combined ventricular output is in the region of 450 ml/kg/min. This figure resembles that found by other workers and the values found in fetal lambs.[6 7] By 32 weeks' gestation, however, when the mean fetal body weight is 2 kg, the combined ventricular output dropped slightly to 420 ml/kg/min. There was a clear pattern for the relation between right and left ventricular outputs. In most cases the output of the right ventricle was higher than that of the left, but in less than a quarter of cases the reverse was true.

There is wide diurnal and individual variation in cardiac output in the normal resting subject, and in the fetus it is difficult to be sure that the measurements are made in a resting state. Doppler tracings are very difficult to obtain if there is appreciable movement of the fetal trunk, but finer head or limb movements are impossible to exclude during the study. Such movements could alter the peripheral resistance, and thus the Doppler estimate of mean velocity, and could contribute to the scatter of normal values.

Despite these reservations about the method these data demonstrate that Doppler echocardiography can be used to study human fetal cardiac function. These normal values provide the basis for the interpretation of data obtained from fetuses with abnormalities of pregnancy, structural heart disease, or cardiac arrhythmias.

We thank Mrs Rosemary Brown, senior lecturer in biostatistics, Guy's Hospital, for her work on the statistical analysis.

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References

1 Allan LD, Tynan MJ, Campbell S, Wilkinson JL, Anderson RH. Echocardiographic and anatomical correlates in the fetus. *Br Heart J* 1980;**44**:444–51.

2 Kleinman CS, Hobbins JC, Jaffe CC, Lynch DC, Talner NS. Echocardiographic studies of the human fetus: prenatal diagnosis of congenital heart disease and cardiac dysrhythmias. *Pediatrics* 1980;**65**:1059–68.

3 Allan LD, Crawford DC, Anderson RH, Tynan MJ. Echocardiographic and anatomical correlations in fetal congenital heart disease. *Br Heart J* 1984;**52**:542–8.

4 Lewis JF, Kuo LC, Nelson JC, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. *Circulation* 1984;**70**:425–31.

5 Meijboom EJ, Horowitz S, Valdes-Cruz LM, Sahn DJ, Larson DF, Lima CO. A Doppler echocardiographic method for calculating volume flow across the tricuspid valve: correlative laboratory and clinical studies. *Circulation* 1985;**71**:551–60.

6 Rudolph AM, Heymann MA. The circulation of the fetus in utero. *Circ Res* 1967;**21**:163–84.

7 Reed KL, Meijboom EJ, Sahn DJ, Scagnelli SA, Valdes-Cruz LM, Shenker L. Cardiac Doppler flow velocities in human fetuses. *Circulation* 1986;**73**:41–6.

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Obstruction of the central pulmonary artery after shunt operations in patients with pulmonary atresia

KAZUO MOMMA,* ATSUYOSHI TAKAO,* YASUHARU IMAI,† HIROMI KUROSAWA†

*From the Departments of *Paediatric Cardiology and †Surgery, the Heart Institute of Japan, Tokyo Women's Medical College, Tokyo, Japan*

SUMMARY The central pulmonary artery was studied angiographically 1–10 years after a palliative operation in 56 patients (mean age 6 years, range 1–20) with congenital heart disease and pulmonary atresia. All of them had originally had a central pulmonary artery that was common to both the right and left pulmonary arteries. Juxtaductal obstruction of the left pulmonary artery had developed in 70% of the patients; in 40% the obstruction was atretic unilaterally. Atresia developed at the right junction to the ductus where there was a shunt to the right pulmonary artery and at the left junction where there was a shunt to the left pulmonary artery. Stenosis causing a reduction of more than 50% of the inner diameter developed at the anastomotic site in 10% of 30 patients with a functioning Blalock shunt. In contrast, there was occlusion of the pulmonary artery or its upper branch in 73% of 11 patients with a non-functioning anastomosis.

Surgical techniques such as the Rastelli[1 2] or the Fontan procedure[3 4] have been developed to treat patients with congenital heart disease, pulmonary atresia, and a central pulmonary artery that is common to both the right and left pulmonary arteries. Palliative operation may be important when further intracardiac repair is planned. We found that juxtaductal obstruction of the left pulmonary artery developed in 67% of 21 patients with pulmonary atresia without a preceding operation.[5] In patients who have had a palliative operation additional stenosis may develop in the central pulmonary artery at the point of surgical intervention. The development and clinical application of our new preformed catheter for selective angiography of the central pulmonary artery in 1981[6] means that atresia of the central pulmonary artery can be visualised more clearly than before. We have investigated obstruction of the central pulmonary artery developing after palliative operation in patients with pulmonary atresia.

Requests for reprints to Dr Kazuo Momma, The Heart Institute of Japan, Tokyo Women's Medical College, Kawada-cho 8-1, Shinjuku-ku, Tokyo 162, Japan.

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Patients and methods

From November 1981 to November 1984, 56 consecutive patients with congenital heart disease and pulmonary atresia were admitted to our institute for cardiac catheterisation 1–10 years after palliative operation. At preoperative aortography contrast medium passed into the central pulmonary artery through the ductus arteriosus. The precise arrangement of juxtaductal pulmonary arteries was not displayed before operation because selective angiography was not available. During the same period 21 similar patients who had not had a palliative operation were studied by selective pulmonary angiography. These were the subject of another study of the course of juxtaductal obstruction of the left pulmonary artery in pulmonary atresia not treated by palliative operation.[5]

We reviewed angiograms and surgical records of the 56 patients who had had a palliative operation. Intracardiac anatomy was diagnosed by cross sectional echocardiography and ventriculography. Table 1 lists the previous operations and intracardiac diagnosis in these 56 patients (aged 1 to 20 years, mean 6). The interval between the previous operation and the present study ranged from one to 10 years (mean 4). Patients with bilateral ductus

Table 1 *Intracardiac anatomy and previous operations in 56 patients with pulmonary atresia*

Intracardiac anomaly	*No operation*	*Palliative operation*				*Total*
		Left Blalock	*Right Blalock*	*Brock*	*Others*	
Fallot's tetralogy	11	11	4	1	8	35
Intact ventricular septum	2	2		2		6
Tricuspid atresia	1	2				3
Univentricular heart	2	4	4		2	12
Ventriculoarterial discordance	3	6	2		2	13
Atrioventricular and ventriculoarterial discordance	1	3	3			7
Atrioventricular septal defect	1					1
Total	21	28	13	3	12	77

arteriosus or major aortopulmonary collateral arteries[7] were excluded from this study.

Angiography of the central pulmonary artery was performed as follows. After ventriculography or aortography, the ductus arteriosus or the surgically created anastomosis was catheterised and selective pulmonary angiography was performed with biplane cinefilm or cut-film equipment. Since November 1981 we have successfully used a preformed catheter[6] for selective injection of contrast medium through the ductus. Pulmonary vein wedge angiography[8-10] was performed to visualise occult pulmonary arteries.

In this article we use the term central pulmonary artery to describe the pulmonary trunk (main pulmonary artery) and the right and the left pulmonary arteries proximal to the hilar portion. In three patients with situs inversus the terms right pulmonary artery or left pulmonary artery relate to the morphology of the vessels. Pulmonary artery stenosis was defined as a reduction of the inner diameter to less than 50% of its largest diameter. The term atresia was applied to obstructions where angiograms showed a sharply demarcated obstruction without wash out of contrast (figs 1 and 2). When the pulmonary artery was generally smaller than normal, this was termed hypoplasia. Two types of pulmonary atresia were identified on the angiograms. In

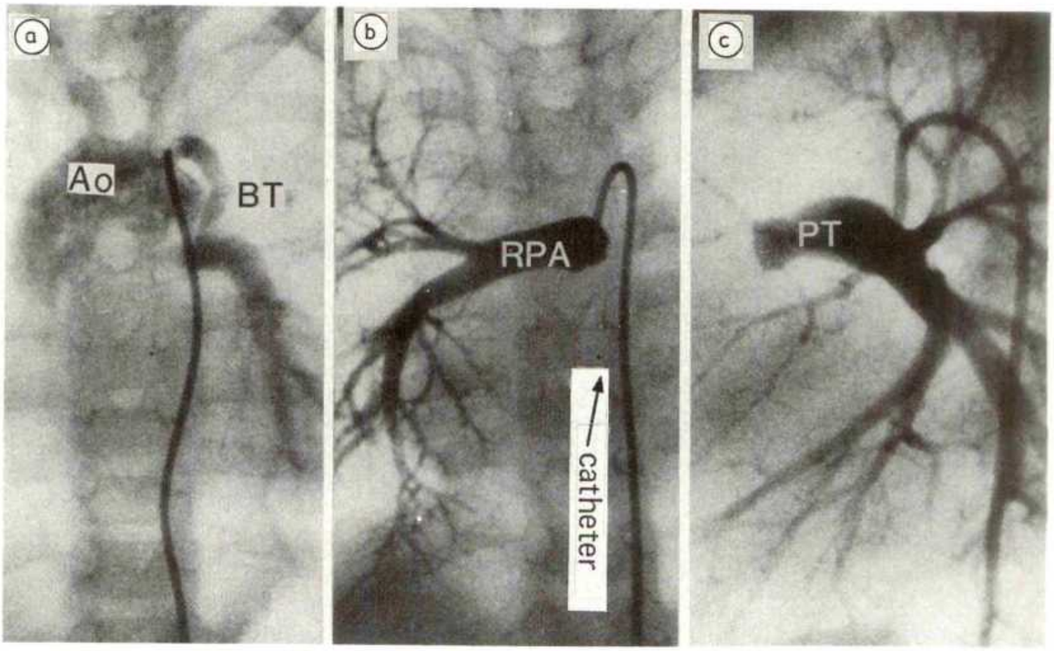

Fig 1 *Pulmonary arteriograms of a two year old boy with tetralogy of Fallot, pulmonary valve atresia, ductus arteriosus, and a left Blalock shunt. Injection at the orifice of the anastomosis showed the left pulmonary artery with an atretic junction to the ductus (a). Selective injection through a preformed catheter into the ductus visualised only the right pulmonary artery and a well developed pulmonary trunk ((b), frontal; (c), lateral). Ao, aorta; RPA, right pulmonary artery; PT, pulmonary trunk; BT, Blalock-Taussig shunt.*

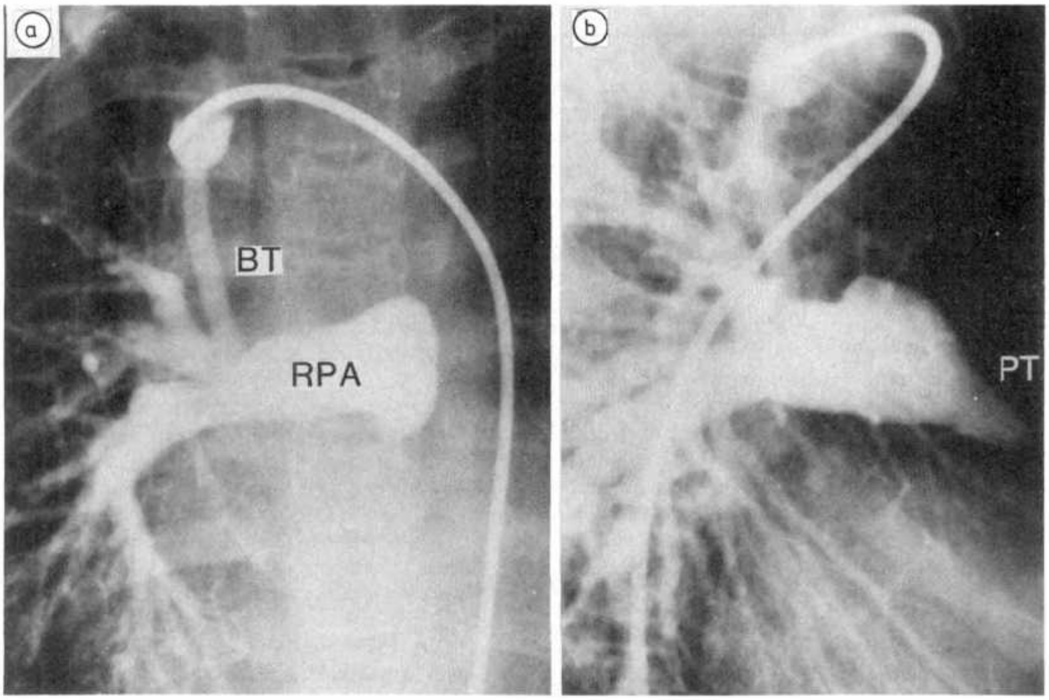

Fig 2 *Pulmonary arteriograms of a 10 year old girl with tetralogy of Fallot, pulmonary trunk atresia, ductus arteriosus, and a right modified Blalock shunt. Injection into the anastomosis visualised the right pulmonary artery and pulmonary trunk ((a), frontal; (b), lateral). Juxtaductal atresia in the left pulmonary artery was diagnosed on the basis of this angiogram. Injection into the ductus, which visualised only the left pulmonary artery (not shown), confirmed the diagnosis. See legend to fig 1 for abbreviations.*

pulmonary valve atresia the pulmonary trunk was long and tubular and sinuses of Valsalva were seen at its anterior end (fig 1). In truncal atresia, the pulmonary trunk was short and cone shaped (fig 2). The ductus was patent at catheterisation in 40 of the 56 patients. The ductus arteriosus was left sided in all 40 patients and originated from the left innominate artery in the 10 patients with right aortic arch.

STATISTICAL ANALYSIS

Differences in proportions were tested by the χ^2 test[11] and a p value of 0·05 was regarded as significant.

Results

Stenosis or atresia in the central pulmonary artery developed either at the junction of the ductus (juxtaductal obstruction[5]) or at the site of the surgical shunt. We did not find stenosis or atresia at any other part of the central pulmonary artery other than the point of surgical intervention. The influence of each surgical intervention on the development of the obstruction in the central pulmonary artery was different and we give the results for each surgical group.

LEFT BLALOCK SHUNT

This group of 28 patients includes those with the original Blalock shunt and a modified Blalock shunt with a polytetrafluoroethylene (PTFE) graft. We found eight patterns of ductus arteriosus and obstructions in the central pulmonary artery (fig 3). Only six (21%) of 28 did not have any obstruction in the central pulmonary artery, 79% had juxtaductal obstruction—in 12 (43%) patients this was atretic. In all but one of these 12 patients juxtaductal atresia was left sided. In this exceptional case the left Blalock shunt was becoming occluded and blood flow through the shunt was much reduced. Blood flow to the left pulmonary artery was maintained from the ductus, and juxtaductal atresia developed in the right side as it did in those patients without previous shunt operation.[5]

In two patients the anastomosis was occluded and the left pulmonary artery was not visualised by contrast medium coming through either the ductus or the anastomosis. Pulmonary vein wedge angio-

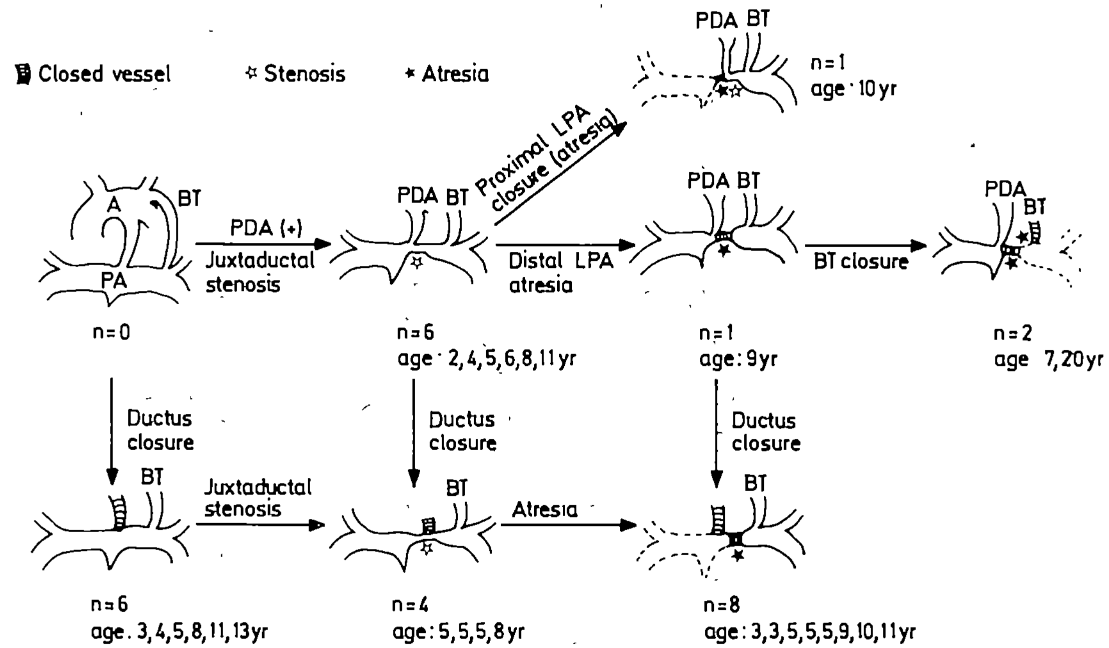

Fig 3 *Patterns of the central pulmonary artery after a left Blalock-Taussig (BT) shunt in 28 patients with congenital heart disease and pulmonary atresia in whom the central pulmonary artery had originally been common to both the right and left pulmonary arteries. Numbers of patients and their ages are given. A, aorta; PA, pulmonary artery; PDA, ductus arteriosus; LPA, left pulmonary artery*

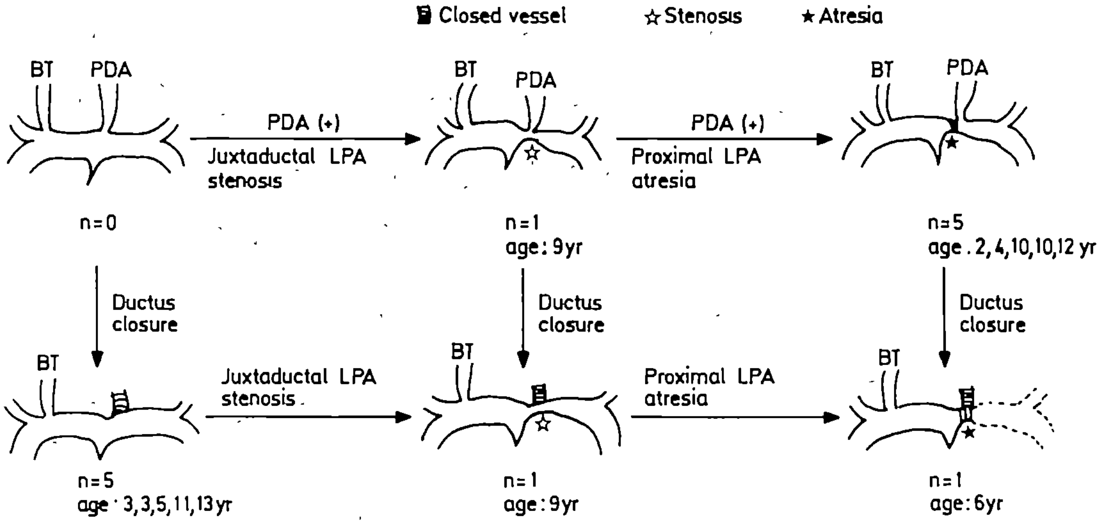

Fig 4 *Patterns of the central pulmonary artery after a right Blalock-Taussig (BT) shunt in 13 patients with congenital heart disease and pulmonary atresia in whom the central pulmonary artery had originally been common to both the right and left pulmonary arteries. Numbers of patients and their ages are given. See legend to fig 3 for abbreviations.*

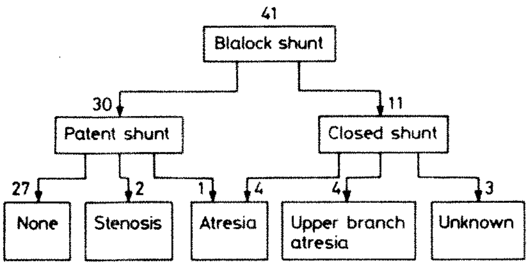

Fig 5 *Frequency of occlusion of the pulmonary artery or its branches at the anastomotic site of Blalock shunt.*

graphy confirmed the patency of the peripheral left pulmonary artery in both patients.

RIGHT BLALOCK SHUNT

There were 13 patients in this group and six patterns of arrangement of the ductus and obstructions in the central pulmonary artery (fig 4). Eight (62%) had juxtaductal obstruction and six of these had atresia. Juxtaductal atresia of the left pulmonary artery always developed to the right of the ductus in this group. A closed ductus with juxtaductal obstruction in the left pulmonary artery was found in only one patient. No patient showed significant obstruction of the right pulmonary artery at the anastomosis.

Figure 5 summarises the type of obstruction that we found in the pulmonary artery at the point of anastomosis in these two groups of patients with Blalock shunts. At the junction of the anastomosis the contour of wall of the pulmonary artery was uneven and the inner diameter was often reduced slightly (fig 2). Stenosis or occlusion developed in only three out of 30 patients with functioning subclavian to pulmonary artery anastomosis, however. In the 11 patients with non-functioning Blalock shunt, there was obstruction of the pulmonary artery or its upper branch (fig 6) in eight (73%) patients. In the remaining three patients we could not visualise this part of the pulmonary artery.

WATERSTON SHUNT

We studied six patients with a Waterston shunt. Three had associated ductus arteriosus and two had a left Blalock shunt. One had had bilateral non-functioning Blalock shunt before Waterston shunt was done. Six patterns of the central pulmonary artery were observed (fig 7). Juxtaductal obstruction of the left pulmonary artery was present in all six,

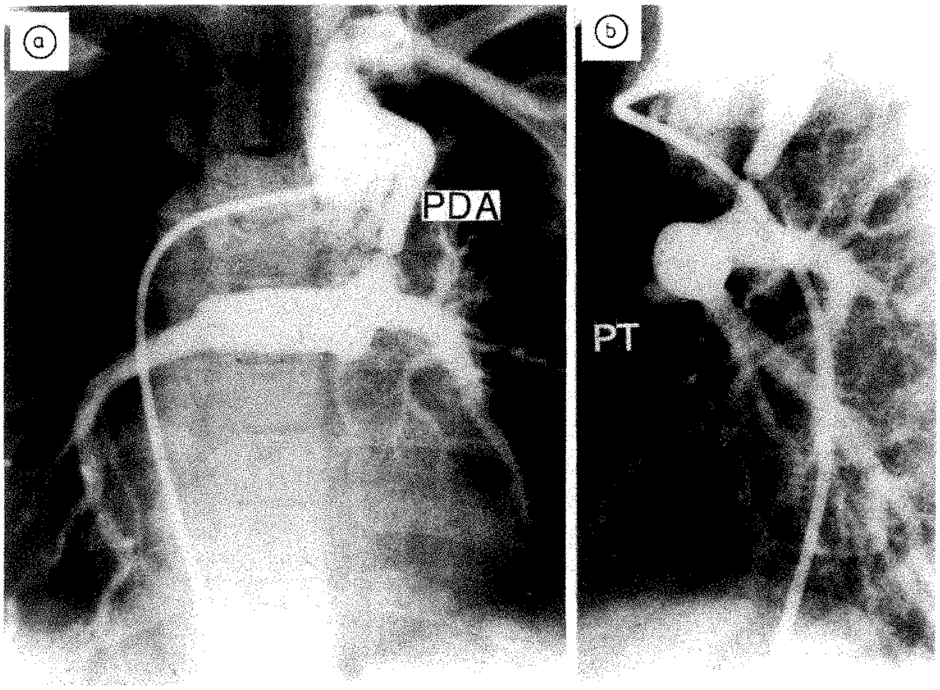

Fig 6 *Pulmonary arteriograms of a seven year old girl with ventriculoarterial discordance, right aortic arch, pulmonary trunk (PT) atresia, ductus arteriosus (PDA), and a non-functioning right Blalock shunt. Injection into the ductus visualised the central pulmonary artery except for its right upper branch which was atretic at the site of the occluded Blalock shunt. (a), frontal; (b), lateral.*

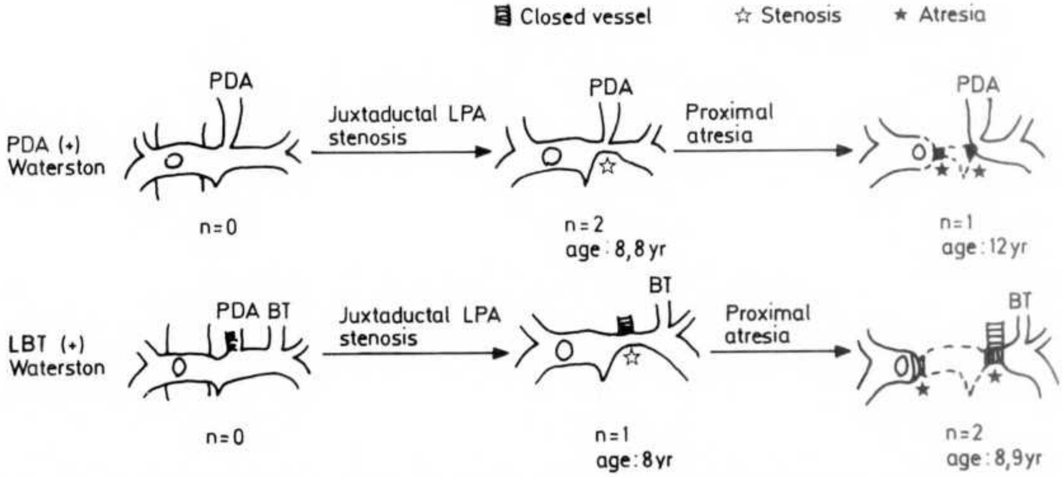

Fig 7 *Patterns of the central pulmonary artery after a Waterston shunt in six patients with congenital heart disease and pulmonary atresia in whom the pulmonary artery had originally been confluent. Numbers of patients and their ages are given. See legend to fig 3 for abbreviations. LBT, left Blalock-Taussig.*

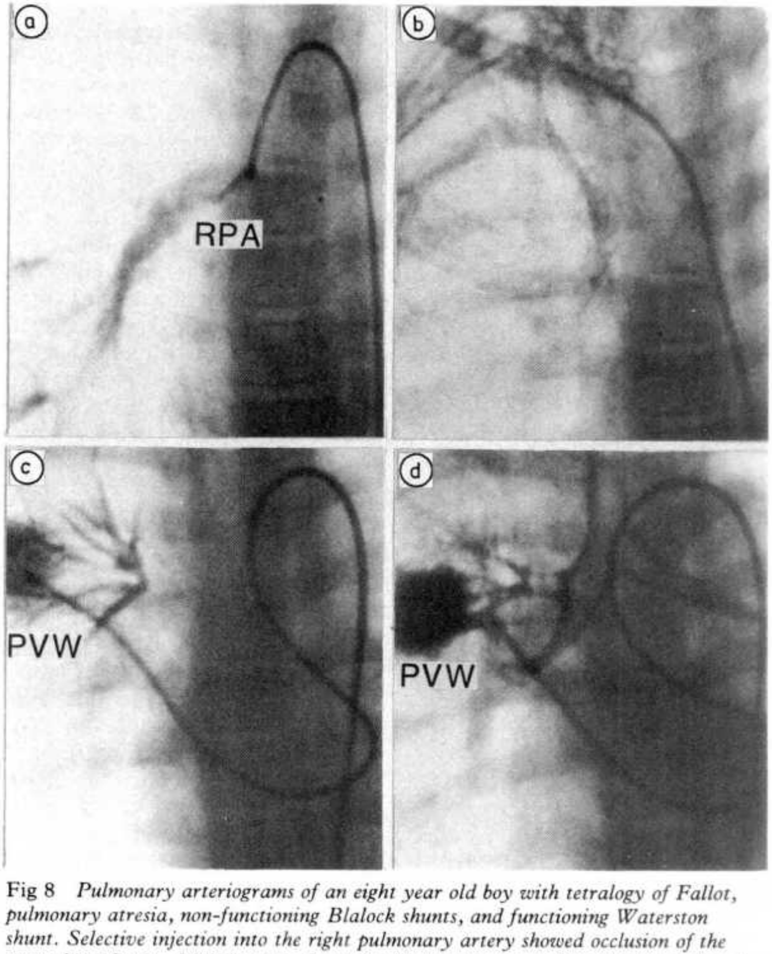

Fig 8 *Pulmonary arteriograms of an eight year old boy with tetralogy of Fallot, pulmonary atresia, non-functioning Blalock shunts, and functioning Waterston shunt. Selective injection into the right pulmonary artery showed occlusion of the upper branch (a). Injection into the right subclavian artery showed well developed collateral vessels and occluded anastomosis (b). Injection into the wedge position of the upper pulmonary vein (PVW) with a transarterial catheter showed atresia of the upper branch of the right pulmonary artery (c), followed by extravasation into the sputum and the appearance of contrast in the bronchi a few seconds later (d).*

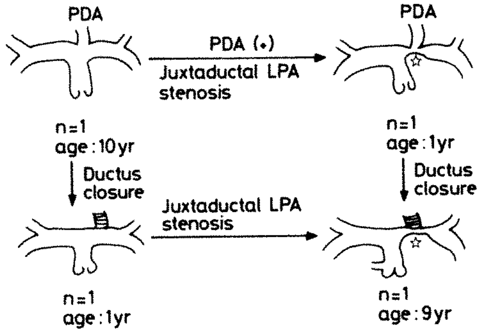

Fig 9 *Patterns of the central pulmonary artery after Brock operation or central shunt in four patients with congenital heart disease and pulmonary atresia in whom the central pulmonary artery had originally been common to both the right and left pulmonary arteries. Numbers of patients and their ages are given. See legend to fig 3 for abbreviations.*

and in three of these there was atresia. At the anastomosis the proximal right pulmonary artery was obstructed completely in three patients (fig 8), and partially in the other three patients.

A complication of pulmonary vein wedge angiography occurred in an eight year old boy with tetralogy of Fallot, pulmonary atresia, bilateral non-functioning Blalock shunts, and a functioning Waterston shunt. Selective right pulmonary arteriography showed complete occlusion of the upper branch and occlusion at the proximal right pulmonary artery. Power injection into the right upper pulmonary vein was associated with intrapulmonary injection, the appearance of contrast in the bronchi, and bloody sputum. Blood disappeared from the sputum within 24 hours and he recovered without any noticeable residual lesion.

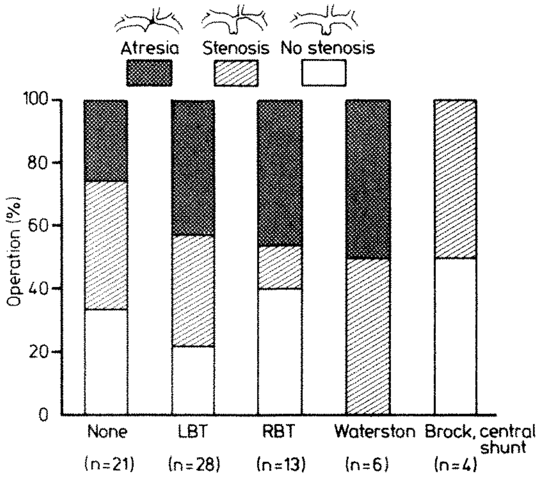

Fig 10 *Frequency of juxtaductal obstructions of the left pulmonary artery in each surgical group and the group not treated by operation. LBT, left Blalock shunt; RBT, right Blalock shunt.*

Table 2 *Numbers and percentages of juxtaductal obstructions in each type of pulmonary atresia in 56 patients 1–10 years after palliative operation*

Juxtaductal obstruction	*Pulmonary valve atresia (%)*	*Pulmonary trunk atresia (%)*	*Type not diagnosed (%)*
No obstruction	10 (48)	5 (28)	0
Stenosis	9 (43)	7 (39)	3 (18)
Atresia	2 (9)	6 (33)	14 (82)
Total	21 (100)	18 (100)	17 (100)

BROCK OPERATION AND CENTRAL SHUNT

We studied three patients with Brock operation and another patient with a central shunt (ascending aortopulmonary artery graft). Figure 9 shows the four patterns of the central pulmonary artery that we found in these patients. Two had juxtaductal stenosis in the left pulmonary artery.

Figure 10 shows the frequencies of juxtaductal stenosis and atresia in each surgical group. We compared these results with data collected from a group of 21 patients who had not had a palliative operation. Juxtaductal stenosis or atresia developed in every group. It was milder in Brock's operation and central shunt, but the small number of patients in this group precludes any definite conclusion.

Table 2 shows how juxtaductal obstruction in these 56 patients correlated with the type of pulmonary atresia. In 17 patients the pulmonary trunk could not be visualised and the type of pulmonary atresia remained unknown. Atresia of the pulmonary valve was associated with less frequent and milder juxtaductal obstruction of the left pulmonary artery than atresia of the pulmonary trunk.

Discussion

In this study and an earlier one,[5] juxtaductal obstruction in the left pulmonary artery was the most common and most major obstruction found in the central pulmonary artery in patients with congenital heart disease and pulmonary atresia in whom the central pulmonary artery had been common to both the right and left pulmonary arteries. This obstruction, however, was modified by the preceding palliative operation. In those patients who had not had a palliative operation[5] with a right Blalock or Waterston shunt, juxtaductal atresia developed to the right of the ductus. In patients with left Blalock shunt, juxtaductal atresia developed on the left side of the ductal junction. In patients who had not had a palliative operation juxtaductal obstruction developed exclusively in those with truncal atresia; no patient with an atretic pulmonary valve had juxtaductal obstruction.[5] This was not true of the 56 patients reported in the present study.

Progressive juxtaductal obstruction was common both in patients with a shunt operation and in those without.[5] Angiography showed a cone-shaped stenosis on both sides of the junction of the ductus and in the left pulmonary artery. In those without shunts this stenosis progressed to atresia after the age of four.[5] In some of those with shunts, however, juxtaductal atresia developed at the age of two or three years. This suggests that a shunt operation may accelerate juxtaductal obstruction of the left pulmonary artery.

In patients with an anastomosis between the left subclavian artery and pulmonary artery, atresia was more common at the left junction. Juxtaductal atresia developed at the left junction in all four patients who had both a ductus arteriosus and had had a well functioning left Blalock shunt for more than a year. The mechanism that causes the development of atresia at the left junction in this particular group is not clear. Presumably, blood flow became turbulent at this point after the establishment of a shunt to the left pulmonary artery and this caused a jet lesion to develop there. The same mechanism could account for the development of atresia at the right junction to the ductus after a shunt to the right pulmonary artery. This mechanism could also explain why juxtaductal obstruction was mild in patients after a Brock operation or central shunt.

We showed a clear correlation between the patency of the anastomosis between the subclavian artery and pulmonary artery and occlusion of the pulmonary artery at the anastomotic site. Significant occlusion at the anastomotic site rarely developed in the pulmonary artery while the anastomosis was functioning, whereas when the anastomosis was not functioning there was invariably occlusion of the pulmonary artery or its branch at this site. This emphasises the importance of a good anastomosis in patients with pulmonary atresia in whom further intracardiac repair is planned.

In patients with atresia of a pulmonary artery at the site of a non-functioning anastomosis, the patency of the peripheral pulmonary artery can be shown by pulmonary vein wedge angiography.[8-10] This technique is not without risk, however. Pulmonary vein wedge angiography should be tried only after careful selection of the injection site, dose of contrast material, and injection speed. We recommend a hand injection of contrast material to visualise an occult upper branch of a pulmonary artery. In patients with one occult pulmonary artery, we recommend injection into the pulmonary vein of the middle or lower lobe. Power injection should only be used after hand injection of a small amount of contrast material has established the presence of a patent peripheral portion of the pulmonary artery.

A Waterston shunt is often associated with occlusion of the right pulmonary artery at a point proximal to the anastomosis.[12 13] This was confirmed in the present study. Obstructive lesions of this type will require careful treatment by angioplasty at intracardiac repair. Occlusion of the right pulmonary artery proximal to the anastomosis also curtails the supply of blood shunted to the left pulmonary artery and this may inhibit development of the vascular bed in the left lung. These aspects should be considered when palliative operations are selected for patients in whom intracardiac repair is planned.

Brock's operation, if technically feasible, is probably the most suitable operation for patients with atresia of the pulmonary valve. A Blalock shunt or modified Blalock shunt is the standard operation for patients with atresia of the pulmonary trunk. There is no known method of preventing the development of juxtaductal obstruction in the left pulmonary artery; however, juxtaductal obstruction in the left pulmonary artery was generally mild in those patients with a spontaneously closed ductus arteriosus. Ligation of the ductus at palliative operation may prevent progress of juxtaductal obstruction in the left pulmonary artery in the neonatal period.

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References

1 Pacifico AD. Pulmonary atresia with VSD. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Corrective surgery*. (Paediatric cardiology 5.) Edinburgh: Churchill Livingstone, 1983:137–43.

2 Moore CH, Martelli V, Ross DS. Reconstruction of right ventricular outflow tract with a valved conduit in 75 cases of congenital heart disease. *J Thorac Cardiovasc Surg* 1976;**71**:11–9.

3 Marcelleti C, Mazzera E, Olthof H, *et al*. Fontan's operation: an expanded horizon. *J Thorac Cardiovasc Surg* 1980;**80**.764–9.

4 Gale AW, Danielson GK, McGoon DC, Mair DD. Modified Fontan operation for univentricular heart and complicated congenital lesions. *J Thorac Cardiovasc Surg* 1979;**78**:831–8.

5 Momma K, Takao A, Ando M, *et al*. Juxtaductal left

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Tricuspid atresia with transposition of the great arteries in adolescents and adults: current state and late complications

CAROLE A WARNES, JANE SOMERVILLE

From the Paediatric and Adolescent Unit, National Heart Hospital, London

SUMMARY The outcome was reviewed in 17 patients aged 15–40 years with tricuspid atresia and transposed great arteries selected by survival beyond age 14 years. Only five lead normal lives (ability index 1 or 2); the rest are dead or disabled. Arrhythmias occurred in seven. Maintenance of sinus rhythm is important because incessant atrial arrhythmias cause serious symptomatic deterioration. Pulmonary vascular disease and subaortic stenosis were important determinants of late mortality and morbidity. Because the mortality associated with the Fontan operation was high in these patients it should be performed with impeccable surgical technique and only in those who fulfil *all* the selection criteria for the operation. A shunt is the preferred option when any of the criteria are not met.

Palliative surgery and the Fontan operation have modified the course of tricuspid atresia and transposed great arteries, but little is known about the outcome in adults with this condition. We have reviewed 17 adolescents and adults with this anomaly and have assessed the factors which contributed to their death and disability.

Patients and methods

We reviewed all patients with angiographically proven tricuspid atresia and transposed great arteries who were seen at the National Heart Hospital, London, since 1965 and who survived beyond age 14 years. The 17 patients (aged 15–40 years) were divided into two groups—group A: 12 patients with palliative shunts or no previous surgery (six are alive to date) and group B: five patients who had a Fontan operation or modification at 15–21 years; only one is alive. The causes of death were analysed and necropsy data were examined when they were available. All living patients were examined in 1986 and had chest *x* ray, electrocardiogram, exercise test by the modified Bruce protocol, and 24 hours of ambulatory electrocardiography. The left ventricular ejection fraction was measured by cross sectional echocardiography and equilibrium electrocardiogram-gated radionuclide angiography. The ability index was determined in each patient to evaluate their quality of life (figure).[1]

Results

GROUP A PATIENTS WITH PALLIATIVE SHUNTS OR NO SURGERY

Table 1 shows the data on 12 patients. Nine had pulmonary stenosis. Two (cases 2 and 5) had shunt operations before the age of one, a further five needed surgery during the first decade, and one had a Blalock-Taussig shunt at 17 years. One patient had her first shunt operation at 34 years. Seven patients had Blalock shunts, two a Glenn anastomosis (cases 5 and 9), and three patients had a direct aortopulmonary anastomosis—Potts (case 2), Waterston (case 12), or from ascending aorta to left pulmonary artery (case 5). Three patients without pulmonary stenosis (cases 4, 7, and 11) survived more than 14 years without surgery, but had severe pulmonary vascular disease and presented with serious symptoms (haemoptysis, severe hypoxia) in the second and third decades. In a fourth patient (case 5) pulmonary vascular disease only developed after three previous shunt procedures, almost certainly as a

Requests for reprints to Dr Jane Somerville, Paediatric and Adolescent Unit, National Heart Hospital, Westmoreland Street, London W1M 8BA.

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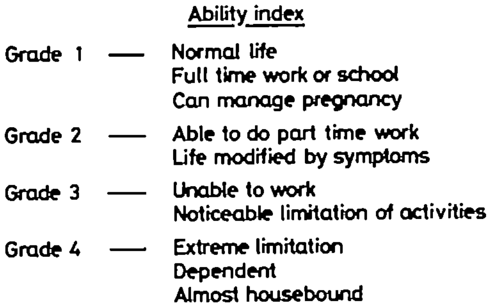

Ability index

Grade 1	—	Normal life Full time work or school Can manage pregnancy
Grade 2	—	Able to do part time work Life modified by symptoms
Grade 3	—	Unable to work Noticeable limitation of activities
Grade 4	—	Extreme limitation Dependent Almost housebound

Figure *Ability index classification.*

result of a direct aorto-pulmonary artery shunt performed when she was eight years old.

Mortality

Six patients aged 15–22 years died—three at operation. One with the Eisenmenger reaction (case 7) had massive haemoptysis from an infarct in the right lung and died after emergency lobectomy. Another with a failing Glenn anastomosis (case 9), small pulmonary arteries, and mild subaortic stenosis died at an attempted Blalock shunt. This was her third operation. The third death occurred in a patient (case 8) with angina, mild aortic valve stenosis, and severe subaortic stenosis; she died in asystole after extensive resection (>4 g) of muscle from the subaortic right ventricle; the ventricular septal defect was large.

Patient 10 died suddenly nine months after an initially successful Blalock shunt performed at the age of 17 years; increasing hypoxia suggested thrombosis of the shunt. A patient (case 12) with an ability index of 2 died from an intracerebral haemorrhage. This was probably caused by habitual glue sniffing; two previous shunts were functioning. Patient 11 died in chronic left ventricular failure with pulmonary vascular disease, mitral regurgitation, and atrial fibrillation.

Survivors: ability index and exercise capacity

Four of the six survivors lead nearly normal lives (ability index of 1 or 2) (table 1). Two patients with pulmonary vascular disease (cases 4 and 5) are more severely limited (ability indices of 3 and 4).

Six patients performed an exercise test; three of the four with no pulmonary vascular disease reached stage III; one (case 2) stopped in stage II. The two patients with pulmonary vascular disease stopped at stage 0.

Left ventricular ejection fraction measured by radionuclide angiography ranged from 36% to 64% (mean 47). Neither of the two patients with impaired ventricular function (cases 3 and 4) have had previous shunts, but both are hypoxic and have polycythaemia that requires regular venesection. One

Table 1 *Clinical data on 12 patients with tricuspid atresia and transposition of the great arteries who had palliative procedures or no surgical treatment*

Case No	*Age*	*Sex*	*Congenital pulmonary stenosis*	*Operations performed and age (yr)*	*Ability index in 1986*	*Arrhythmias*	*LVEF (%)*	*Pulmonary vascular disease*	*Cause of death*
Alive.									
1	40	F	+	Blalock shunt (dextrocardia) (34)	2	AF	64	0	—
2*	28	F	+	Potts anastomosis (1)	2	Multifocal AT	52	0	—
3	27	M	+	Pulmonary valvotomy (7)	2	0	36	0	—
4	26	F	0	0	4	VT	38	+	—
5	22	F	+	Blalock shunt (2/12) Glenn anastomosis (3) Ascending Ao-LPA shunt (8)	3	0	49	+ Acquired late	—
6	20	M	+	Blalock shunt (6)	1	0	45	0	—
Dead·									
7	22	M	0	R lower lobectomy (22)		0		+	Operative
8†	22	F	+	Blalock shunt (2) Resection of subaortic stenosis (22)		Couplets, VPCs		0	Operative Asystole
9†	18	F	+	Blalock shunt (4) Glenn anastomosis (12) Blalock shunt (18)		0		0	Operative. Failed shunt
10	17	F	+	Blalock shunt (17)		0		0	9/12 later. Failin shunt
11‡	17	M	0	0		AF		+	Inoperable
12	15	M	+	Blalock shunt (3) Waterston anastomosis (14)		0		0	1 yr later. Intracerebral haemorrhage

*This patient has subsequently had a Fontan operation. †Patients 8 and 9 also had subaortic stenosis. ‡Patient 11 also had mitral regurgitation.
AF, atrial fibrillation, Ao, aorto, AT, atrial tachycardia; LPA, left pulmonary artery, LVEF, left ventricular ejection fraction; R, right; VPCs, ventricul premature complexes; VT, ventricular tachycardia

Table 2 *Clinical data on five patients with tricuspid atresia and transposition of the great arteries with a Fontan procedure*

Case No	*Age*	*Sex*	*Congenital pulmonary stenosis*	*Previous operation and age (yr)*	*Age at Fontan*	*Type of Fontan*	*Ability index*	*Arrhythmia*	*LVEF (%)*	*Cause of death*
Alive										
13	18	F	+	Pulmonary valvotomy (5), Potts anastomosis (11)	18	Direct RA appendage to PA	2	Bigeminy	26	—
Dead.										
14*	25	M	+	Blalock shunt (6)	19 25	Dacron tube + homograft RA to PA				Reoperation. Thrombus in conduit + PAs. Right PA stenotic beyond conduit
15	24	M	+	Blalock shunt (9)	21	Homografts RA to PA (×2) = 2 outlets from RA. Inflow homograft IVC		VT, paced		Bleeding at cardiac transplantation
16	18	F	+	Blalock shunt (2)	15 18	PAs remade with Dacron + homograft RA to PA				Reoperation (2nd day). Poor PA development
17*	15	M	+	Blalock shunt (2)	15	Homografts RA to PA (×2) = 2 outlets from RA. VSD enlarged				2nd day. Cerebral anoxia. Intractable arrhythmias

*Patient 14 also had severe subaortic stenosis and patient 17 also had moderate aortic stenosis.
IVC, inferior vena cava, LVEF, left ventricular ejection fraction, PA, pulmonary artery, RA, right atrium, VT, ventricular tachycardia, VSD, ventricular septal defect

(case 4) has pulmonary vascular disease. Despite measurable impairment of ventricular function the other (case 3) has an ability index of 2.

Arrhythmias

Five of the 12 patients had arrhythmias. Atrial fibrillation caused symptomatic deterioration in two, which improved in one (case 1, who also had a transient stroke) after cardioversion. She has remained in sinus rhythm on quinidine for four years. In three patients asymptomatic arrhythmias were found on Holter monitoring: non-sustained multifocal atrial tachycardia (case 2), non-sustained ventricular tachycardia (case 4), and ventricular couplets (>30/h) (case 8).

GROUP B. PATIENTS WITH A FONTAN OPERATION

Table 2 summarises the data on these five patients. All had pulmonary stenosis. Four had had a Blalock shunt in the first decade, and one (case 13) had had a pulmonary valvotomy and a Potts shunt. All patients had improvement in their clinical state after the shunt operation. A Fontan operation, with various modifications, had been performed at 15–21 years (table 2).

Mortality

There were four deaths, three in patients who were not ideal candidates for the procedure. Three who died at reoperation had not had symptomatic benefit from the Fontan operation. Patient 14, with small pulmonary arteries and severe subaortic stenosis, developed severe right-sided congestion and eventually his conduit and pulmonary arteries became thrombosed. He died at reoperation. Patient 15 had adequate preoperative left ventricular function, but heart block developed at operation and he required an epicardial pacemaker. He was well enough to return to work (ability index 2) but left ventricular function deteriorated. One year after the Fontan operation ventricular tachycardia developed. This was abolished by amiodarone. His ejection fraction fell to 10% and cardiac transplantation was performed, but he died from uncontrollable bleeding. Patient 16 had poor pulmonary artery development and despite refashioning of the pulmonary arteries with Dacron and a homograft right atrial pressure was high after the Fontan procedure and increased over the next three years. At reoperation the pulmonary arteries were again refashioned but the right atrial pressure remained high (20 mm Hg) and she died on the second postoperative day. A 15 year old boy died on the second day after a Fontan operation. Before operation he had moderate subaortic stenosis (gradient 40 mm Hg at rest) with a left ventricular end diastolic pressure of 20 mm Hg and a pulmonary artery pressure of 34/24 mm Hg.

Survivor: ability index and exercise capacity

One patient (case 13) was alive nine months after the Fontan operation. She had an ability index of 2, left ventricular ejection fraction was 26%, and Holter monitoring showed runs of bigeminy. She reached stage II of the exercise test and was stopped by dyspnoea.

Discussion

Tricuspid atresia and transposition of the great arteries is uncommon, and without early surgery the prognosis is usually poor[2] because of hypoxia from low pulmonary blood flow in those with pulmonary stenosis or left ventricular failure in those with high pulmonary blood flow. In this series, however, two patients with pulmonary stenosis survived to 17 and 34 years without surgical treatment, and two paitents with the Eisenmenger reaction survived to 22 and 26 years without surgical intervention. The proportion of patients with this anomaly who survive to adolescence is unknown. The patients we saw were referred to the National Heart Hospital because they had complications and because of our known interest in adult congenital heart disease.

Most patients (16/17 (94%)) had sufficient pulmonary blood flow to survive the first year without surgery, but 71% (12/17) needed a shunt or pulmonary valvotomy in the first decade. Perhaps those who require surgical treatment in infancy rarely survive to adolescence because they have severe pulmonary stenosis or atresia or a small ventricular septal defect.

Pulmonary vascular disease was common (4/17 patients) and was an important determinant of late mortality and morbidity. In three patients with no pulmonary stenosis (cases 4, 7, and 11) the Eisenmenger state developed early; two died before 22 years of age, and the survivor is severely disabled. In one patient (case 5) pulmonary hypertension developed over a decade after an ascending aorta to left pulmonary artery anastomosis had been constructed when she was 8; she now has an ability index of 3. When left ventricular failure developed in adults with tricuspid atresia, pulmonary congestion rapidly accelerated their deterioration, and they are unlikely to survive to the fourth decade.[3]

The option of cardiopulmonary transplantation is more hazardous in those with previous operations because they are liable to have torrential bleeding from the chest wall during further operation. Many would argue that pulmonary artery banding should be performed in patients with heart failure in infancy to keep the pulmonary vascular resistance low, so that the Fontan procedure, considered by many to be the ultimate operation of choice for this condition, can be performed later. We are not convinced, however, that such patients with a Fontan operation performed at an early age would survive to their early twenties. Also early surgery in such patients virtually rules out subsequent successful cardiopulmonary transplantation. Furthermore, there is no doubt that in infants with heart failure, pulmonary artery banding accelerates the development of subaortic stenosis.[4] This is why we perform pulmonary artery banding only when failure is uncontrollable or if the chest has to be opened for repair of a coarctation.

Subaortic stenosis is a serious acquired lesion, which when it is severe may cause angina (case 8). It may develop under the aorta in the subaortic "conus" or at the ventricular septal defect.[5] Those who have subaortic stenosis at birth, or soon after, are unlikely to survive to the second decade.[3] Four of the patients we describe had subaortic stenosis of varying degrees and two died after attempted relief of the obstruction. We believe that the outlook in patients with subaortic stenosis is poor despite the introduction of new operations. It should be assumed that sympathetic stimuli will increase the gradient. The effect of isoprenaline should be measured at the time of cardiac catheterisation to confirm this. If left ventricular function is sufficiently good we believe that β blockade may offer less hazardous short term symptomatic relief of subaortic stenosis than surgery.

Arrhythmias were common (7/17) and occurred irrespective of the type of operation and even when no operation had been performed. Thus arrhythmias appears to be part of the normal course, as they are in tricuspid atresia with normally related great arteries.[1] Atrial arrhythmias occurred in three patients and ventricular arrhythmias in four. Neither arrhythmia was more common in those with impaired left ventricular function. Incessant atrial fibrillation, however, causes serious symptomatic deterioration and it is important to attempt early cardioversion. Medical treatment has maintained sinus rhythm in all survivors, but left ventricular function must be watched if negative inotropes are used. In one patient complete heart block developed after a Fontan operation at 21 years of age and he needed a pacemaker; the epicardial route was chosen.

Although impairment of left ventricular ejection fraction might be expected in patients with longstanding shunts, all survivors with shunts had normal ejection fractions, but their left ventricular cavities were large. Left ventricular ejection fraction did not correlate with exercise capacity, which was impaired in all patients, but despite this all patients without pulmonary vascular disease led nearly normal lives as judged by the ability index.

Should adolescents and adults with shunts or pulmonary valvotomy be referred for a Fontan operation while haemodynamic function is good—that is when they have an ability index of 1 or 2? Unfortunately, we cannot answer this question because three of our five patients did not meet the ideal criteria for Fontan; however, the one who was an ideal candidate (case 15) did badly. The mortality of the Fontan operation in those with transposed great arteries is certainly higher than it is in those with simple tricuspid atresia,[1] and this should be borne in mind when referral of a symptom free adult for this procedure is considered. It could be argued that the patients in this series had their Fontan operations performed relatively late in life and that this may also have adversely affected the outcome.[6 7] We do not know whether they would have survived to adulthood if the Fontan operation had been performed earlier. We are not convinced that such patients will live longer or have less disability if they have a Fontan operation. When haemoglobin rises or symptoms become worse in patients who fulfil all the criteria for a Fontan operation they are referred for the operation. We accept that there are greater risks after a Fontan operation and more complications than after a shunt; however, the potential long term benefits may be better. Few patients in this age group will meet all the criteria, mainly because earlier palliative shunts will have been performed too late or will be too large or technically imperfect. Even when only one criterion is not fulfilled the mortality and morbidity of a Fontan operation appear to be unacceptable, and in this circumstance we prefer a shunt, even though they too are associated with added risks and difficulties in these young adults with long term cyanosis. To reduce these difficulties an impeccable surgical technique is required to construct a shunt of ideal size that does not distort the pulmonary arteries or use Dacron, which leads to thromboses. The shunt should be large enough to reduce hypoxia, yet not be too large and overload the left ventricle.

These results are depressing. We recognise that these patients were treated at a time of pioneering surgical efforts and that mistakes were made. This report illustrates the diversity of difficulties encountered in such patients. Even having learnt from our mistakes, we suspect that because of the problems inherent in the anomaly we will still not be able to prevent disabling illness in many adult survivors with tricuspid atresia and transposition of the great arteries.

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References

1 Warnes CA, Somerville J. Tricuspid atresia in adolescents and adults: current state and late complications. *Br Heart J* 1986;56:535–43.
2 Patel R, Fox K, Taylor JFN, Graham GR Tricuspid atresia. Clinical course in 62 cases (1967–1974). *Br Heart J* 1978;40:1408–14.
3 Patterson W, Baxley WA, Karp RB, Soto B, Bargeron LL. Tricuspid atresia in adults. *Am J Cardiol* 1982;49:141–52.
4 Freedom RM, Benson LN, Smallhorn JF, Williams WG, Trusler GA, Rowe RD. Subaortic stenosis, the univentricular heart, and banding of the pulmonary artery: an analysis of the courses of 43 patients with univentricular heart palliated by pulmonary artery banding. *Circulation* 1986;73:758–64.
5 Somerville J. Congenital heart disease—changes in form and function. *Br Heart J* 1979;41:1–22.
6 Fontan F, Choussat A, Brom AG, Chauve A, Deville C, Castro-Cels A. Repair of tricuspid atresia. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology*. Edinburgh: Churchill-Livingstone, 1977· 567–80.
7 Sanders SP, Wright GB, Keane JF, Norwood WI, Castaneda AR. Clinical and hemodynamic results of the Fontan operation for tricuspid atresia. *Am J Cardiol* 1982;49:1733–40.

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Results of surgical repair for dissection of the ascending aorta

A J MURDAY, R PILLAI, P G MAGEE, R K WALESBY, J E C WRIGHT, M F STURRIDGE

From the London Chest Hospital

SUMMARY Between 1970 and 1986, 40 patients had surgical treatment for dissection of the ascending aorta at the London Chest Hospital. The overall hospital mortality was 27·5%. Preoperative renal impairment and age $\geqslant$60 years were both associated with a significantly increased hospital mortality. In the long term one patient was lost to follow up. There have been two late deaths among the remaining 28 patients (mean follow up 4·4 years). The functional state of the survivors is good, with only three having any cardiac disability.

Aortic dissection was first described by Sennertus in 1628.[1] In 1769 Morgagni deduced that the condition arose as a result of blood forcing its way through the layers of the aortic wall.[2] The earliest attempts at surgical repair were unsuccessful,[3 4] until 1955, when DeBakey *et al* described an operation in which the false lumen was obliterated and aortic continuity restored by means of a graft.[5] This, together with measures to combat complications of the condition such as aortic incompetence and major vessel occlusion, remains the rationale behind the surgical management of aortic dissection.

We have analysed the early and late results of surgical repair for dissection of the ascending aorta at the London Chest Hospital from 1970 up to February 1986. There is still debate about the ideal treatment for dissection of the descending aorta.[6] It is our policy to use medical management for dissections confined to the descending aorta.

The classification developed by DeBakey and his coworkers[7] defines type I dissections as those which affect the ascending and descending aorta, type II dissections as affecting only the ascending aorta, and type III dissections as starting distal to the origin of the left subclavian artery and not extending retrogradely. Miller *et al* group dissections of types I and II together as type A and they call type III dissections type B.[6] In this report we have adopted the classification of Miller *et al*.

Patients and methods

We analysed the case notes of all patients who had undergone surgery for aortic dissection since 1970, noting the details of preoperative history, clinical state, and laboratory results. We also examined operation records to determine the nature of the operative intervention, noting postoperative complications. Hospital survivors were traced. Those still alive were contacted by telephone and asked a series of questions about their current state of health. The cause of death in patients who died after operation was obtained from the records of their family practitioners and, where relevant, from the records of other hospitals.

Fisher's exact probability test was used to determine whether or not various preoperative factors had any statistically significant effect upon hospital mortality.

Results

PATIENTS

Forty patients (29 M, 11 F), aged 17–74 (mean 55), had surgical treatment for dissection of the ascending aorta.

AETIOLOGY

Hypertension was the most common aetiological factor. Fifteen (38%) patients had hypertension before operation. Two (5%) cases were the direct result of cardiac catheterisation. Two patients had clear stigmata of Marfan's syndrome, and one case occurred 10 days after aortic valve replacement. The

Requests for reprints to Dr A J Murday, The London Chest Hospital, Bonner Road, London E2 9JX.

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Table 1 *Operative procedures*

Operation	*No*
Aortic graft alone	17*
Aortic repair alone	7*
Aortic graft with valve repair	9
Aortic graft with valve replacement	2
Aortic repair with valve repair	1
Aortic repair with valve replacement	3
No procedure	1

*In each of these categories one patient had concurrent coronary artery surgery.

largest group, consisting of 19 (48%) patients, had no obvious aetiological factors.

DIAGNOSIS

In most patients dissection was diagnosed by aortography (34/40), while two cases were undiagnosed preoperatively and one was diagnosed by plain chest *x* ray. Recently we have been assessing the role of digital subtraction aortography after intravenous injection of contrast; three patients had the repair operation after this investigation alone.

ANATOMICAL TYPE

Of the 40 patients with type A dissections that make up this series, 25 were operated upon within two weeks of the onset of symptoms (acute) and 15 beyond two weeks (chronic).

PREOPERATIVE PROCEDURE

Table 1 summarises the operative procedures. Before 1978 coronary perfusion was used and thereafter cardioplegic arrest. One of the 40 patients died before cardiopulmonary bypass could be established. Two patients underwent concurrent coronary artery bypass grafting.

HOSPITAL MORTALITY

There were 11 hospital deaths; thus the overall hospital survival rate was 72·5%. Table 2 gives the causes of death. In the single case in which it proved impossible to establish cardiopulmonary bypass all the femoral perfusion entered the false lumen, compressing and occluding the branches of the aortic arch; the patient died.

Table 2 *Causes of hospital mortality*

Cause	*No*
Haemorrhage	4
Cardiorespiratory failure	3
Cerebral embolus	1
Intestinal infarction	1
Renal failure	1
Unable to establish bypass	1

Table 3 *Hospital mortality related to preoperative complications and other factors*

	Hospital mortality
Age	
<60 yr	4/28 (14%)
≥60 yr	7/12 (58%)
Renal impairment:	
Present	6/9 (67%)
Absent	5/31 (16%)
Year of operation	
Up to 1977	5/10 (50%)
After 1977	6/30 (20%)
Haemopericardium:	
Present	5/12 (42%)
Absent	6/28 (21%)
Aortic incompetence	
Present	6/26 (23%)
Absent	5/14 (36%)

RISK FACTORS

The relation of several preoperative indices to hospital mortality was examined to identify factors that affected operative risk (table 3).

(a) year of operation—Between 1970 and 1977, 10 patients underwent surgical repair for aortic dissection. Over this period hospital mortality was 50%. Between 1978 and 1986 30 patients had surgical repair and six (20%) died in hospital after the operation. This difference does not quite reach statistical significance ($p = 0·08$) (Fisher's exact test).

(b) Renal impairment—Nine patients had renal impairment (raised plasma urea or creatinine or urine output <20 ml/hour) before operation. In this group hospital mortality was 6/9 (67%) compared with 5/31 (16%) in those patients without renal impairment. This difference is statistically significant by Fisher's exact probability test ($p < 0·05$).

(c) Age—Twelve of the 40 patients were ≥60 years at operation. The mortality for this group was 7/12 (58%) compared with 4/28 (14%) for patients who were <60 at operation. This difference just reaches statistical significance (Fisher's test, $p = 0·05$).

(d) Haemopericardium was present at operation in 12 patients; however, this finding had no statistically significant effect upon hospital mortality. Five patients with haemopericardium died, compared with six of the 28 without haemopericardium.

(e) Aortic valve regurgitation—There was evidence of aortic regurgitation in 26 patients before operation and six (23%) of these patients died within 30 days of operation. Five (36%) of the 14 patients without evidence of aortic incompetence died. This difference is not statistically significant.

(f) Sex—The hospital mortality for male patients was 7/28 (25%) and that for female patients was 4/12 (33%). This difference is not statistically significant.

EARLY NON-FATAL COMPLICATIONS

Five serious non-fatal complications occurred within the early postoperative period. One patient suffered paraplegia which did not resolve. Hemiplegia developed in another patient, who made a complete recovery. There was a single episode of retinal infarct, resulting in a partial field defect in one eye, that did not resolve. Endocarditis caused by *Staphylococcus aureus* developed in one patient. This was successfully treated with antibiotics. The fifth patient developed acute renal failure after septicaemia, which was successfully treated without long term sequelae.

LONG TERM FOLLOW UP

One patient was lost to follow up immediately after hospital discharge. All the other 28 hospital survivors have been followed up to the present time. The average time from operation to the present is 4 4 years. There have been two late deaths. One patient with Marfan's disease died two years after his original operation (aortic repair) having undergone two subsequent aortic root replacements. The other died from heart failure five years after operation (aortic valve replacement and aortic repair). Three further patients suffered events that may be related to the original aortic dissection. One patient developed aortic regurgitation requiring aortic valve replacement four years after valve resuspension and ascending aorta repair for an acute dissection. This patient is well 2·5 years later. One patient had an abdominal aortic aneurysm repaired three years after repair of a chronic dissection. A third patient suffered a right hemiplegia two years after ascending aortic replacement with a Dacron graft for a chronic dissection. Of the 26 known long term survivors, 23 are symptom free and in the other three activity is slightly restricted by cardiovascular disability. Twelve patients are in full time employment.

Discussion

Hospital mortality associated with surgical treatment of type A aortic dissection is high, but that associated with medically treated patients is higher.[8] Opinion is divided on the relative merits of surgical and medical treatment of type B aortic dissection. Whereas DeBakey and his collegues in Houston advocate surgical treatment for these patients,[7] there is considerable evidence that elsewhere the results of medical management are just as good.[9 10] This is why at the London Chest Hospital patients with aortic dissections of the ascending aorta (type A) are treated surgically, and those with dissections that are restricted to the descending aorta (type B) are treated medically.

Like others,[11 12] we found a history of systemic hypertension in most patients presenting with aortic dissection. The only other notable aetiological factors were Marfan's disease and trauma at either angiography or cardiac surgery.

The preferred method of preoperative diagnosis will always depend upon the facilities available within the unit. Direct aortography has become the established method, but computerised tomography,[13] magnetic resonance,[14] and digital subtraction aortography after intravenous injection of contrast[15] are alternatives. Recently, we have been using digital subtraction aortography as a first line method of diagnosis at the London Chest Hospital. So far three patients have had a repair operation after this investigation alone.

What information does the surgeon require to treat an aortic dissection? Confirmation of diagnosis is essential. Whether the site of the intimal tear must be known is open to question. The site of the tear is irrelevant if the only object of the operation is to restore the integrity of the lumen of the ascending aorta and the aortic valve. Many surgeons argue that coronary angiography is required so that incidental coronary artery disease may be recognised and treated. There is no evidence available upon which to base a rational decision about the merits of bypass grafting for these incidental lesions. We find that diagnosis established by digital subtraction angiography after intravenous injection of contrast is sufficient in most cases.

The surgical procedures used vary with time and between different surgeons. The principles of the surgical intervention, however, remain constant. These are restoration of the integrity of the ascending aortic wall by oversewing the two layers with or without an interposition graft and reestablishment of aortic competence when necessary, either by aortic valve replacement or by resuspension of the aortic valve when possible.

In common with other reports,[16 17] several preoperative factors were found to affect outcome significantly. Patients aged $\geqslant 60$ had over three times the hospital mortality of those aged <60. Preoperative renal impairment also trebled the hospital mortality. Perhaps not surprisingly, hospital mortality has fallen progressively with time; however, the difference between the two periods (1970–1977 and 1978–1986) does not reach statistical significance. Neither the presence of haemopericardium or regurgitation at the aortic valve affected surgical outcome.

For hospital survivors (72·5% of those who underwent surgery) the prospects of a return to full activity were good. Only one patient was lost to follow up. Two patients have died, both from cardiovascular causes. But the vast majority of the long term survivors (23 out of 26) reported that their activity was not restricted by cardiovascular disability; and 12 patients were in full time employment. Since the average age of all the patients at the time of operation was 55 years, a large proportion of those not in full time employment are now beyond retirement age.

References

1 Shennan T. *Dissecting aneurysms*. (Medical Research Council Special Report Series No 193.) London: HMSO, 1934.

2 Morgagni JB. *The seats and causes of diseases investigated by anatomy*, vol 1. (Alexander B, translator) London: A Miller, T Cadele, 1769:808–9.

3 Paullin JE, James DF. Dissecting aneurysms of the aorta. *Postgrad Med* 1948;4:291–9.

4 Johns TNP. Dissecting aneurysm of the abdominal aorta. Report of a case with repair by perforation. *Ann Surg* 1953;137:232–5.

5 DeBakey ME, Cooley DA, Creech O Jr. Surgical considerations of dissecting aneurysm of the aorta. *Ann Surg* 1955;142:586–612.

6 Miller DG, Stinson EB, Oyer PE, *et al.* Operative treatment of aortic dissections. *J Thorac Cardiovasc Surg* 1979;78:365–82.

7 DeBakey ME, McCollum CH, Crawford S, *et al.* Dissection and dissecting aneurysms of the aorta. Twenty year follow-up of five hundred twenty-seven patients treated surgically. *Surgery* 1982;92.1118–34.

8 Wheat MW, Harris PD, Malm JR, Kaiser G, Bowman FO, Palmer RF. Acute dissecting aneurysms of the aorta. Treatment and results in 64 patients. *J Thorac Cardiovasc Surg* 1969;58:344–51.

9 Anagnostopoulos CE. Medical therapy of acute aortic dissection. Introduction. In: Anagnostopoulos CE, Athanasuleas CL, Garrick TR, Palissian RB, eds. *Acute aortic dissections*. Baltimore: University Park Press, 1975:209–11.

10 Dorghazi RM, Slater EE, DeSanctis RW. Medical therapy of aortic dissection. *Cardiovasc Med* 1981;6: 187–98.

11 Wilson SK, Hutchins GM. Acute dissecting aneurysms. Causative factors in 204 subjects. *Arch Pathol Lab Med* 1982;106:175–80.

12 Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. *Am J Cardiol* 1984;53:849–55.

13 Moncada R, Churchill R, Reynes C. Diagnosis of dissecting aortic aneurysm by computed tomography. *Lancet* 1981;i:238–41.

14 Amparo EG, Higgins CB, Hricak H, Sollitto R. Aortic dissection: magnetic resonance imaging. *Radiology* 1985;155:399–406.

15 Guthaner DF, Miller DC. Digital subtraction angiography of aortic dissection. *American Journal of Roentgenology* 1983;141:157–61.

16 Miller DC, Mitchell RS, Oyer PE, Stinson EB, Jamieson SW, Shumway NE. Independent determinants of operative mortality for patients with aortic dissection. *Circulation* 1984;70(suppl I): I-153–64.

17 Doroghazi RM, Slater EE, DeSanctis RW, Buckley MJ, Austen WG, Rosenthal S. Long-term survival of patients with treated aortic dissection. *J Am Coll Cardiol* 1984;3:1026–34.

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Isolation of the left common carotid or left innominate artery

LANCE V FONG, ALEXANDER W VENABLES

From the Department of Cardiology, Royal Children's Hospital, Victoria, Australia

SUMMARY Isolation of the left common carotid or left innominate artery from the aortic arch is rare. A six week malformed infant with a right aortic arch had isolation of a left innominate artery and connection to the pulmonary artery by a left ductus arteriosus. A right ductus arteriosus had been ligated. Another infant with a right aortic arch and ostium primum atrial septal defect was shown to have an aberrant left subclavian artery arising from the lower descending aorta. The left common carotid artery filled retrogradely and drained into the pulmonary artery by a left ductus arteriosus. This abnormality has not been reported before.

Many forms of aortic arch abnormalities have been described.[1 2] Isolation of a left subclavian artery with connection to the pulmonary artery by a ductus arteriosus has been reported,[3] but isolation of the left innominate artery from a right aortic arch and connection to the pulmonary artery by a ductus arteriosus is rare. Isolation of the left common carotid artery from a right aortic arch with an aberrant left subclavian artery has not been described before. We report one case of a right aortic arch with isolation of the left innominate artery and bilateral ductus and another of isolation of the left common carotid artery with an aberrant left subclavian artery.

Case reports

PATIENT 1

The first case was a six week old female infant with the CHARGE association (colobomata, choanal atresia, retarded growth and development, hearing deficit, and micrognathia). She was tachypnoeic with full peripheral pulses and a continuous murmur at the upper sternal edge consistent with a ductus arteriosus. Cross sectional echocardiography demonstrated a right aortic arch with normal intracardiac anatomy and a large ductus. After ligation of a right ductus a continuous murmur persisted at the upper sternal edge. Doppler echocardiography revealed persisting turbulence in the main pulmonary artery. Aortography revealed early filling of three major vessels arising from the right aortic arch: the right common carotid, the right vertebral, and right subclavian arteries. These vessels joined plexuses of vessels in the neck, mediastinum, and right and left scapular areas. The left common carotid artery was noted filling late from above. Dye passed

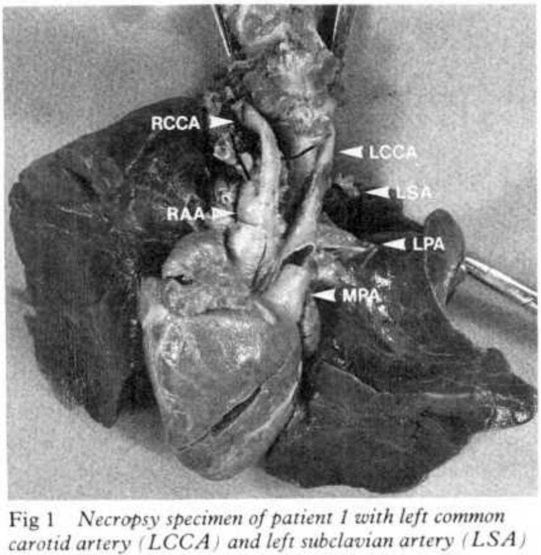

Fig 1 *Necropsy specimen of patient 1 with left common carotid artery (LCCA) and left subclavian artery (LSA) entering the left pulmonary artery (LPA) via a ductus arteriosus. The right common carotid artery (RCCA) arises from the right aortic arch (RAA). MPA, main pulmonary artery.*

Requests for reprints to Dr Alexander W Venables, Department of Cardiology, Royal Children's Hospital, Parkville, Victoria 3052, Australia.

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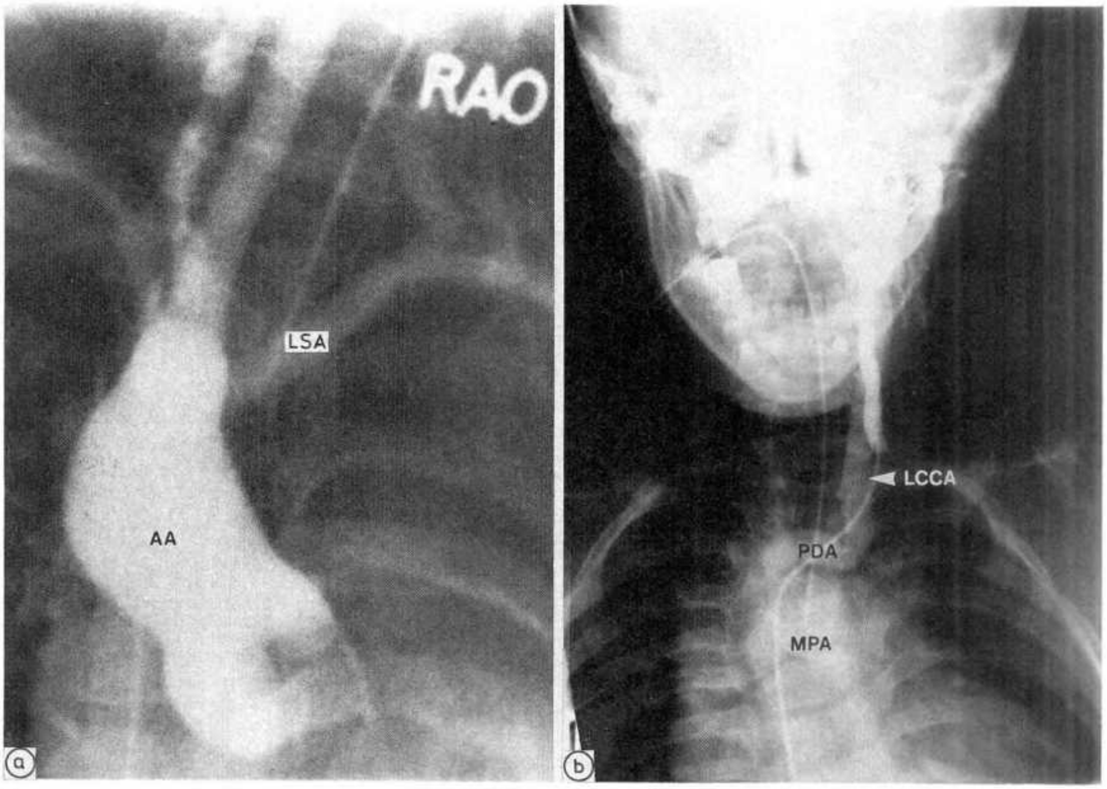

Fig 2 *(a) Aortogram (right anterior oblique view) of patient 2 shows the left subclavian artery (LSA) arising from the lower descending aorta. AA, ascending aorta. (b) Selective angiogram in the left vertebral artery via the aberrant left subclavian artery demonstrates late retrograde filling of the left common carotid artery (LCCA). Dye passes to the main pulmonary artery (MPA) via a ductus arteriosus (PDA).*

from the plexuses into the left subclavian and left vertebral artery, which then joined the left common carotid artery. The left innominate artery then emptied into the left pulmonary artery, presumably via a left ductus. Dye could be seen spilling into both pulmonary arteries. This created a left to right shunt at the pulmonary artery level. There was no vascular ring.

Elective implantation of the left innominate artery to the ascending aorta was planned to remove the left to right shunt and prevent a steal syndrome. The infant died suddenly at home at six months of age. Necropsy confirmed the described abnormality of aortic arch vessels (fig 1) and the normal intracardiac structure. The vessels of the right neck and upper limb were connected to the left innominate artery by the circle of Willis and by collaterals in the neck and both scapular areas. The cause of death remained uncertain. The heart, brain, and other organs were normal.

PATIENT 2

A 10 month old female infant with primordial dwarfism presented with signs suggestive of a ductus arteriosus. Cardiac catheterisation showed an ostium primum atrial septal defect with a right aortic arch and a late filling and a left sided vessel entering the left pulmonary artery from the head and neck vessels. At five years of age follow up angiography demonstrated the right aortic arch from which arose the right common carotid, right subclavian, and vertebral arteries. An aberrant left subclavian artery arose from the right lower descending aorta (fig 2a). Selective injection of the right common carotid, right vertebral, and left vertebral artery via the aberrant left subclavian artery (fig 2b) showed late retrograde flow into the left common carotid artery, which received blood from the circle of Willis, vertebro-basilar system, and costocervical collaterals. There were no arteriovenous malformations in the cranium. Dye passed from the left common

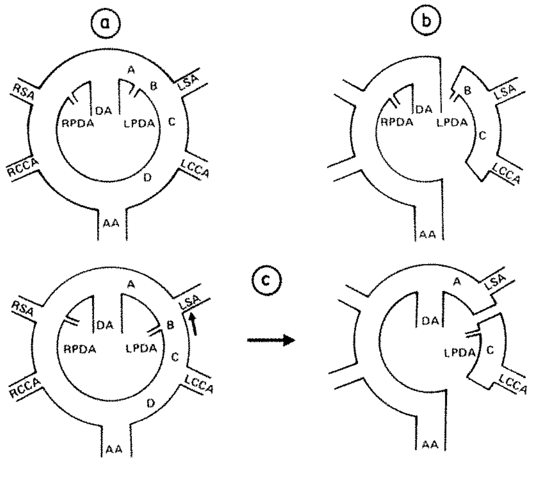

Fig 3 *(a) The hypothetical double arch of Edwards.*[7] *(b) Interruption of the left arch in zones A and D with persistence of the left and right ductus allows development of the aortic arch of patient 1. There is a right aortic arch with isolation of the left innominate artery and bilateral patent ductus. (c) Distal migration of the left subclavian artery beyond the left ductus and concurrent interruption of the left arch in zones B and D would explain development of the aortic arch of patient 2. There is a right aortic arch with isolation of the left common carotid and aberrant left subclavian artery. AA, ascending aorta; DA, descending aorta; LCCA, left common carotid artery; RCCA, right common carotid artery; LSA, left subclavian artery; RSA, right subclavian artery; LPDA, left ductus arteriosus; RPDA, right ductus arteriosus.*

carotid into the left pulmonary artery by a ductus arteriosus, creating a left to right shunt. This vessel was selectively outlined by passing a catheter from the pulmonary artery through the left ductus. There was no right patent ductus and no vascular ring.

The isolated left common carotid artery was ligated. The ostium primum atrial septal defect was repaired and a large left superior vena cava draining into the upper pole of the left atrium was channelled to the right atrium. Postoperative progress was uneventful.

Discussion

The Edwards' hypothetical double aortic arch explains aortic arch abnormalities by selective regression of various parts of either arch[1] (fig 3a). Right aortic arch with isolation of a left innominate artery connecting to the left pulmonary artery by a left ductus has been described rarely.[4, 5] Complete separation with regression of the left ductus arteriosus and the late development of a subclavian steal syndrome has also been reported.[6] These abnormalities can be explained by interruption at two sites in the double aortic arch—in the left posterior arch distal to the ductus and in the left anterior arch proximal to the left common carotid artery. The first infant had this abnormality with bilateral ductus arteriosus (fig 3b).

The second abnormality of isolation of the left common carotid artery with an aberrant left subclavian artery has not been described before. An explanation based on the Edwards' model is that distal migration of the left subclavian artery leading to the left ductus that enters the left dorsal aortic root just proximal to the origin of the left subclavian artery produces concurrent isolation of the left common carotid and an aberrant left subclavian artery. Interruption could occur in the left anterior arch proximal to the left common carotid and distal to the left patent ductus but proximal to the left subclavian artery and left dorsal aortic root (fig 3c). The variable proximity of origin of the left subclavian artery and ductal area has been noted in other conditions such as coarctation of the aorta.[2]

Late filling of left neck vessels providing a left to right shunt into the pulmonary artery was recognised fortuitously in both children, who had associated non-cardiac abnormalities. In both patients elective surgery was planned to prevent a later steal syndrome.[3, 6]

We thank Dr D W Boldt, Director of Radiology, Royal Children's Hospital, Victoria, and Dr C W Chow, anatomical pathologist, Royal Children's Hospital, Victoria, Australia, for their help.

References

1 Stewart JR, Kincaid OW, Edwards JE. *An atlas of vascular rings and related malformations of the aortic arch system.* Springfield, Illinois: Charles C Thomas, 1964:3–13, 80–129.

2 Freedom RM, Culham JAG, Moes CAF. Vascular rings and associated anomalies. In: *Angiocardiography of congenital heart disease.* New York: Macmillan, 1984:487–513.

3 Nath PH, Castaneda-Zuniga W, Zollikofer C, *et al.* Isolation of a subclavian artery. *Am J Roentgenol* 1981;**137**:683–8.

4 Karczenski K, Wozniewicz B. Abnormal site of origin of the common carotid and left subclavian arteries. *Pol Tyg Lek* 1978;**33**:1041–2.

5 Martin EC, Mesko ZG, Griepp RB, Haller JO, Gordon DH. Isolation of the left innominate artery, a right arch and a left patent ductus arteriosus. *Am J Roentgenol* 1979;**132**:833–5.

6 Garti IJ, Aygen MM. Right aortic arch and isolation of the left innominate artery from the aorta. *Cardiovasc Intervent Radiol* 1982;**5**:235–7.

7 Edwards JE. Anomalies of derivatives of aortic arch system. *Med Clin North Am* 1948;**32**:925–49.

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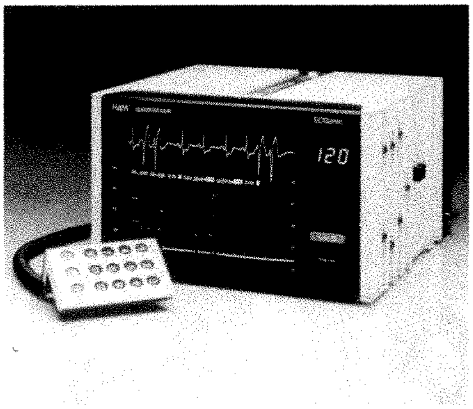

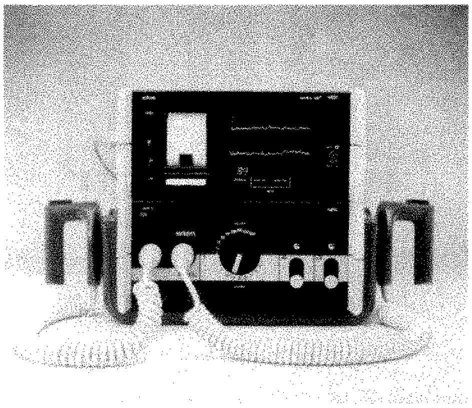

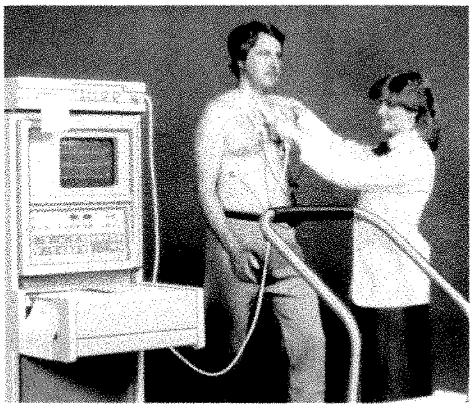

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A case of respiratory sinus arrhythmia and vasovagal attacks: use of cosinor analysis for diagnosis and for monitoring treatment

G R PAI, JOHN M RAWLES

From the Department of Medicine, University of Aberdeen

SUMMARY An 18 year old girl presented with frequent vasovagal attacks and sinus arrhythmia. The amplitude of respiratory sinus arrhythmia assessed by cosinor analysis was 20%; the predicted value for a normal girl of this age is 4% and the 95% confidence interval is 0–8%. Treatment with propantheline, in a dose sufficient to reduce the amplitude of sinus arrhythmia to normal, abolished her symptoms.

Increased vagal tone is a recognised cause of syncope and near syncope[1]; it occurs more commonly in young people or in trained athletes.[2 3] The diagnosis of this condition usually rests on the clinical presentation together with evidence of vagotonia on the electrocardiogram, and it depends on electrophysiological studies for confirmation.[4 5] We report a patient in whom vagal tone was increased and in whom the diagnosis was made by quantifying the amplitude of respiratory sinus arrhythmia on a three minute electrocardiogram by means of cosinor analysis by microcomputer.

Patient and methods

ELECTROCARDIOGRAM RECORDING

In order to minimise voluntary hyperventilation, the subject was not told that her respiration was to be observed. A three minute electrocardiogram was recorded at a paper speed of 50 mm/s from standard lead I with the patient supine during normal spontaneous respiration. Movement of the chest was observed throughout the recording and the event marker was pressed in the pause at the end of each expiration.

We measured the P–P intervals and their relation to end expiratory points using a digitising pad and microcomputer with a resolution of 0·1 mm; the results were stored on disc.

COSINOR ANALYSIS

Cosinor analysis was used to demonstrate the respiratory variation of heart rate. The best fit of a cosine function curve to the cyclical variation of P–P intervals was found by multiple regression analysis. The duration of each respiratory cycle was taken as 360°, with both 0 and 360 signifying end expiratory points. The timing of each P wave in the respiratory cycle in which it occurred was expressed as an angular measure (t). The duration of the associated P–P interval was expressed as a percentage of the mean P–P interval for the whole three minute sequence and this was regressed against cos(t) and sin(t) to give the amplitude, phase angle, and statistical significance of respiratory variation of the P–P interval, forced into the form of a cosine function curve. Cosinor analysis was described by Halberg *et al*[6] and its application to electrocardiogram intervals will be reported by Pai *et al*.[7]

Example

An 18 year old student radiographer presented in March 1985 with a five month history of blackouts which had latterly been occurring three or four times a day. They invariably occurred when she was standing, and from her description there was no reason to think that the blackouts were other than vasovagal attacks, but their frequent occurrence was inconvenient. There were no other symptoms and no previous medical complaints.

The pulse rate was 60 beats per minute and irregular; blood pressure was 100/60 mm Hg with no pos-

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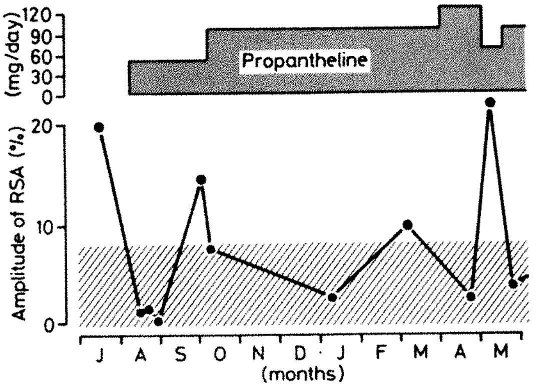

Figure *Amplitude of respiratory sinus arrhythmia (RSA) assessed by cosinor analysis in a patient aged 18 with vagotonia. The hatched area represents the 95% confidence interval for a normal subject of this age.*

tural drop. Physical examination was otherwise normal, and carotid sinus massage did not provoke symptoms or cause undue bradycardia. The electrocardiogram was normal but Holter monitoring showed pronounced sinus arrhythmia, intermittent first degree heart block, and one episode of Wenckebach phenomenon.

In July 1985 cosinor analysis of a three minute electrocardiogram recorded during spontaneous respiration showed respiratory sinus arrhythmia with an amplitude of 20·1%, well outside the normal range. At age 18 the predicted normal value is 4·3%, with a 95% confidence interval of 0·4–8·3%.[7]

Propantheline 15 mg three times a day rapidly relieved the symptoms and reduced the amplitude of sinus arrhythmia, which in August 1985 was 2% (figure). In October 1985 vasovagal attacks recurred and the amplitude of respiratory sinus arrhythmia was again excessively high (15%). Her symptoms responded to an increase in the dose of propantheline to 30 mg three times a day. The amplitude of sinus arrhythmia immediately fell to 8%, and there was a further fall to 3% over the next three months. In May 1986 she complained about the number of tablets she was taking and an attempt was made to reduce the dosage. She had attacks of near syncope and the amplitude of sinus arrhythmia increased to 23%. The daily dosage of propantheline was increased again to 90 mg with relief of symptoms and a reduction in the amplitude of sinus arrhythmia to a normal value of 4%. Throughout the 10 month period of treatment with propantheline she had a dry mouth and eye discomfort in bright sunshine, but she preferred these side effects to frequent vasovagal attacks.

Discussion

Respiratory sinus arrhythmia is mediated reflexly. Because the cardiac vagus nerves are the efferent arm of this reflex sinus arrhythmia is an index of vagal cardiac outflow[8] and increased vagal tone might be expected to exaggerate sinus arrhythmia. Although there is no mention of sinus arrhythmia in recent papers on vagotonia in which diagnosis was by electrophysiological study,[4 5] some older textbooks mention the association of sinus arrhythmia, dizzy spells, and faintness.[9] Electrophysiological study has a low yield of abnormal findings in patients with unexplained syncope when the electrocardiogram is reported to be normal,[10] but respiratory sinus arrhythmia is a normal finding at all ages and an abnormally increased amplitude could be easily overlooked.

Electrophysiological studies in 10 patients with vagotonia by Benditt *et al* showed that intravenous and oral theophylline had positive chronotropic and dromotropic effects.[4] An oral preparation was tolerated by eight of their patients and suppressed symptoms in six during a follow up of from five to 24 months. McLaran *et al* described 12 patients with symptoms similar to our patient. The diagnosis of vagotonia was made by an electrophysiological study in these 12 patients.[5] They were treated with propantheline, which was beneficial in nine cases; the average period of follow up was 23 months.

In our patient the symptoms and Holter monitor findings were highly suggestive of increased vagal tone and the finding of exaggerated respiratory sinus arrhythmia also supported this diagnosis. The diagnosis was confirmed by the patient's response to propantheline. This relieved symptoms and reduced the amplitude of respiratory sinus arrhythmia to normal.

Measurement of the amplitude of respiratory sinus arrhythmia from a three minute electrocardiogram is not only helpful in making a positive diagnosis of vagotonia, but also in monitoring the efficacy of treatment. It is non-invasive, may be repeated as often as required, and is quicker and more simple than electrophysiological study.

We thank Mrs Joy McKnight for invaluable technical assistance. She is supported by a research grant from Grampian Health Board.

References

1 Glick G, Yu PN. Hemodynamic changes during spontaneous vasovagal reactions. *Am J Med* 1963;**34**: 42–51.

2 Strasberg B, Lam W, Swiryn S, *et al*. Symptomatic spontaneous paroxysmal AV nodal block due to local-

ised hyper-responsiveness of AV node to vagotonic reflexes. *Am Heart J* 1982;**103**:795–801.

3 Meytes I, Kaplinsky E, Yahini JH, Hanne–Paparo N, Neufeld HN. Wenckebach AV block: a frequent feature following heavy physical training. *Am Heart J* 1975;**90**:426–30.

4 Benditt DG, Benson DW Jr, Kreitt J, *et al*. Electrophysiological effects of theophylline in young patients with recurrent symptomatic bradyarrhythmias. *Am J Cardiol* 1983;**52**:1223–9.

5 McLaran CJ, Gersh BJ, Osborn MJ, *et al*. Increased vagal tone as an isolated finding in patients undergoing electrophysiological testing for recurrent syncope: response to long term anticholinergic agents. *Br Heart J* 1986;**55**:53–7.

6 Halberg F, Johnson EA, Nelson W, Runge W, Sothern R. Autorhythmometry—procedures for physiologic self-measurements and their analysis. *Physiology Teacher* 1972;**1**(4):1–11.

7 Pai GR, Reid SR, Rawles JM. A method of quantifying sinus arrhythmia: parallel effect of respiration on P–P and P–R intervals. Unpublished.

8 Eckberg DL. Human sinus arrhythmia as an index of vagal cardiac outflow. *J Appl Physiol* 1983;**54**:961–6.

9 Bellet S. *Clinical disorders of the heart beat*. Philadelphia: Lea and Febiger, 1971:142.

10 Gulamhusein S, Naccarelli GV, Ko PT, *et al*. Value and limitations of clinical electrophysiological study in assessment of patients with unexplained syncope. *Am J Med* 1982;**73**:700–5.

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Case report

Long term survival and late repair of massive cardiac pseudoaneurysm

YOAV TURGEMAN,* TIBERIO ROSENFELD,* DAVID A HALON

*From the Departments of Cardiology, *Central Emeq Hospital, Afula, and Lady Davis Carmel Hospital, Haifa, Israel*

SUMMARY Myocardial rupture of the left ventricle after an acute myocardial infarction resulted in the formation of a massive pseudoaneurysm in a middle aged man. Cross sectional echocardiography was useful in identifying the defect which was successfully closed at operation nine years after its formation.

Rupture of the left ventricular free wall during acute myocardial infarction usually leads to haemopericardium, cardiac tamponade, and sudden death.[1] Long term survival without early surgical intervention is rare,[2] but in some patients the rupture leads to the formation of a pseudoaneurysm. We report a patient who survived for an unusually long time after myocardial rupture and the formation of a massive pseudoaneurysm.

Case report

A 56 year old man presented with advanced congestive heart failure and recurrent pulmonary oedema. Nine years before he was admitted to hospital with acute transmural myocardial infarction. The electrocardiogram showed that the lateral wall was the site of infarction. The chest *x* ray on admission showed a normal sized heart with mild pulmonary congestion. One week later the patient suffered repeated episodes of chest discomfort followed by sudden circulatory collapse, extreme cyanosis, and paroxysmal atrial fibrillation. Recurrent pulmonary embolism was diagnosed and he was treated by intravenous fluids and heparin. The chest *x* ray showed progressive cardiac enlargement but there were no new electrocardiographic changes or an increase in cardiac enzyme activity. In the next nine years progressive heart failure developed which was characterised by recurrent episodes of pulmonary oedema. At admission physical examination showed a blood pressure of 110/60 mm Hg and atrial fibrillation with a ventricular response of 80–90 beats/min. The jugular venous pressure was elevated to 20 cm above the sternal angle and showed a prominent V wave. There were signs of pulmonary hypertension and severe right heart failure with prominent ascites and anasarca. In addition, coarse rales were heard over both lungs. Examination of the heart revealed a dyskinetic apex that was displaced to the anterior axilliary line, an apical pansystolic murmur grade 3/6 radiating to the axilla, and a third heart sound. A continuous to and fro murmur was present in the left midaxillary line in the third and fourth intercostal space. The electrocardiogram showed atrial fibrillation, left axis deviation, and signs of old lateral myocardial infarction (fig 1). The chest *x* ray showed a considerably enlarged heart (cardiothoracic ratio of 0·65) and pulmonary venous hypertension. Fluoroscopy showed mild pericardial calcification along the left lateral cardiac border.

Echocardiography revealed a very large multiloculated pseudoaneurysm of the left ventricle communicating with the left ventricular cavity through a defect in the basal lateral myocardial wall (fig 2). The ventricle itself was moderately enlarged and there was reduced global contractility. There were no primary valve abnormalities.

At cardiac catheterisation the mean right atrial pressure was 12 mm Hg (1·6 kPa), right ventricle 50/6–14 mm Hg (6·7/0·8–1·9 kPa), pulmonary artery 50/20 mm Hg (6·7/2·7 kPa), and the wedge pressure was 26 mm Hg (3·5 kPa) with a V wave of 40 mm Hg (5·3 kPa). The forward cardiac index was low (1·6 l/min/m^2). Selective coronary angiography demonstrated total occlusion of the left circumflex

Requests for reprints to Dr David A Halon, Department of Cardiology, Lady Davis Carmel Hospital, 7 Michal Street, Haifa 34362, Israel.

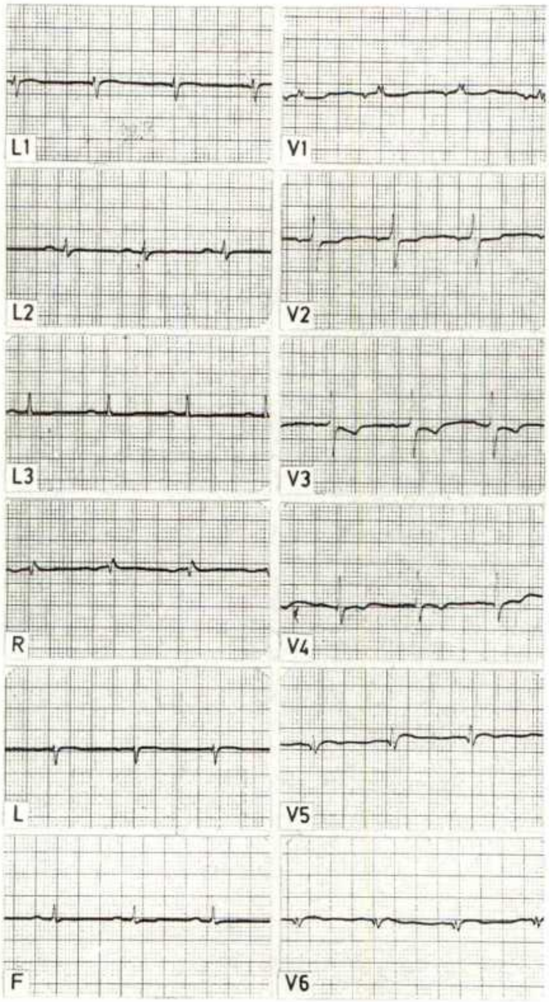

Fig 1 *Electrocardiogram at admission. There are small q waves and loss of R waves in the lateral leads, indicating lateral wall infarction.*

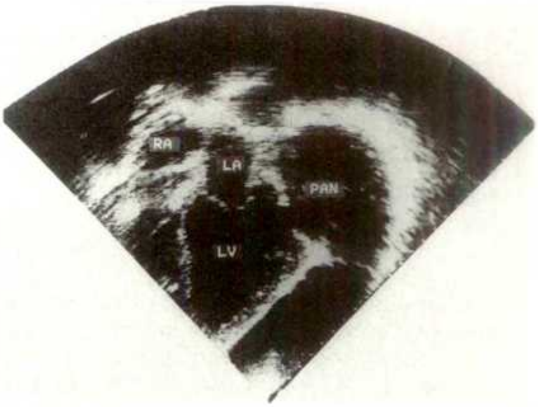

Fig 2 *Cross sectional echocardiogram (apical four chamber view). There is a large multiloculated pseudoaneurysm (PAN) which extends around the anterolateral wall of the left ventricle to its apex. The neck of the pseudoaneurysm communicates with the left ventricular cavity (LV) through the discontinuity in the basal anterolateral wall. RA, right atrium; LA, left atrium.*

artery and a 60% narrowing of the proximal left anterior descending artery with no other important coronary disease. Left ventriculography showed large volumes of dye passing from the left ventricle into the pseudoaneurysm.

At operation a multiloculated pseudoaneurysm with numerous adhesions was found. The location of the myocardial rupture on the posterolateral aspect of the left ventricular free wall close to the posterior papillary muscle confirmed the echocardiographic appearance. The mitral valve itself was not directly affected by the pathological process. At operation the perforation was covered with a Teflon patch and after a rather long convalescence the patient returned to daily activity and a sedentary occupation. Three months after operation he was limited only by particularly strenuous activity (New York Heart Association functional class II).

Discussion

Free wall rupture is believed to occur in 0·5–3·1% of patients after acute myocardial infarction.[3] Myocardial rupture usually causes sudden death; the formation of a false aneurysm is quite rare.[4] Without early surgical intervention long term survival of patients with myocardial rupture is rare[2, 5] and most reports emphasise the need for very early recognition of this complication and immediate vigorous treatment. Pseudoaneurysm formation, while temporarily limiting the course of myocardial rupture, itself produces important haemodynamic complications, including a low cardiac output due to regurgitation of blood into the pseudoaneurysm (analogous to true cardiac aneurysms). In addition, true or functional incompetence may occur after malfunction of the mitral valve apparatus, and in patients with very large pseudoaneurysms the extra volume contained within the pericardium may add an element of compression which can simulate cardiac tamponade. Moreover, since the wall of the pseudoaneurysm is composed of clot, connective tissue, and fibrosis, this tissue may not contain the rupture permanently and it is common for recurrent leakage and sealing off of a pseudoaneurysm to produce the multiloculations—as were found in this patient. Uncontrolled leakage causes death.

To our knowledge this report is the first to describe a patient who survived myocardial rupture for nine years before surgical closure of the defect was performed. In this patient pseudoaneurysm formation was remarkedly advanced and there was gross cardiac disability. The formation of smaller pseudoaneurysms may be more common than is generally appreciated. Wider use of echocardiography in patients after myocardial infarction may increase the recognition of these defects. The echocardiogram is a useful method of making the diagnosis of pseudoaneurysm and in distinguishing pseudoaneurysm from true ventricular aneurysm.[6] The diagnosis of ventricular pseudoaneurysm should be borne in mind in patients who have unusual physical signs, unusual cardiomegaly, or disproportionate cardiac failure after myocardial infarction.

References

1 Alpert J, Braunwald E. Acute myocardial infarction: pathological, pathophysiological and clinical manifestation. In: *Heart disease, textbook of cardiovascular medicine.* 2nd ed. Philadelphia: WB Saunders, 1984:1268–70.

2 Nunez L, de la Llana R, Sendon J, Coma I, Aguado G, Lawes J. Diagnosis and treatment of subacute free wall ventricular rupture after infarction. *Ann Thorac Surg* 1983;**35**:525–9.

3 Vroom RJAF. Myocardial rupture after acute myocardial infarction [Letter]. *Br Heart J* 1984;**51**:98.

4 Fox AC. Infarction and rupture of the heart. *N Engl J Med* 1983;**309**:551–3.

5 Feneley MP, Chung VP, O'Rourke MF. Myocardial rupture after acute myocardial infarction. Ten year review. *Br Heart J* 1983;**49**:550–6.

6 Adamick R, Sprecher D, Coleman RE, Kisslo J. Pseudoaneurysm of the left ventricle. *Echocardiography* 1986;**3**:237–51.

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Proceedings of the British Cardiac Society

At the 66TH ANNUAL GENERAL MEETING of the British Cardiac Society held in Dundee at Ninewells Hospital, on Wednesday and Thursday, 8 and 9 April 1987, E Sowton succeeded D G Julian as President and the following members were elected to Council: A Henderson, I Hutton, A S Hunter, on the retirement of C P Aber, M J Godman, and M Stephens.

The President asked the Society to rise in memory of the following members who died during the previous year: K Shirley-Smith, D Pickering, H Neufeld, A W W B Woods, and A G W Whitfield.

New members joining the Society were as follows: T Aherne (Cork); G Angelini (Cardiff); D B Barnett (Leicester); P Bloomfield (Edinburgh); W Brawn (Australia); J L Caplin (Southampton); J F Cleland (London); A B Davies (Penarth); B M Fabri (Liverpool); R K Firmin (Leicester); J L Gibbs (Bramham); H H Gray (Kingston upon Thames); H M Husaini (Stockport); B S Jenkins (London); A Lahiri (Harrow); B Lewis (London); D P Lipkin (Harrow); H G Love (Altrincham); D P Nicholls (N Ireland); A D C Norris (Faversham); R J Northcote (Glasgow); C R Nyman (Boston); T H Pringle (Belfast); A C Rankin (Glasgow); D B Rowlands (Wirral); A Rozkovec (Bristol); J H Silas (Wirral); P L C Smith (London); N C Taylor (Dyfed); S R Underwood (London); J M Walker (Oxford).

An announcement was made of the importance of the social programme for the Society's Jubilee meeting to be held at Wembley on the 24 to 26 November 1987. There will be plenary sessions on Great British Cardiologists of the Past and Cardiology for the Future.

During the meeting the scientific sessions were held under the chairmanship of H Watson and D Emslie-Smith and the following are abstracts of the papers that were presented.

Balloon aortic valvuloplasty: high frequency of early recurrence of aortic stenosis

M Dancy, D Redwood, C W Pumphrey, D E Ward
Cardiology Department, St George's Hospital, London

Eight patients aged 68 to 89 underwent nine balloon aortic valvuloplasty procedures, three from the brachial and the remainder from the femoral route. Balloon sizes ranged from 1·2 cm to 2·1 cm triple lumen and two patients had the double balloon technique. A significant (> 30%) fall in peak to peak aortic valve gradient was recorded immediately after eight procedures. The calculated aortic valve area (thermodilution cardiac output) increased in five out of six patients. Doppler estimates of aortic valve gradients were made before and one to two days after the procedure and showed significant improvement (> 30%) in only one patient. This patient was the only one to show sustained symptomatic benefit. Another had relief of angina for two days. One patient had a small stroke two hours after the procedure. Five patients subsequently had aortic valve replacement. Three valves were bicuspid and two were tricuspid. No evidence of valve disruption was apparent at operation. In two patients the epicardial surface of the left ventricle was bruised: in one bruising on the anterior surface was associated with a large pericardial haematoma and in the other the bruise was at the apex. In the patient who had suffered the stroke there was thrombus at the apex of the left ventricle. Operation was complicated by anterior myocardial infarction in one patient and a major stroke in another.

We conclude that balloon aortic valvuloplasty is a relatively safe procedure but that it may produce only temporary deformation of the aortic valve orifice which quickly returns to its original shape. Improvement in haemodynamic function during the procedure does not imply lasting benefit.

Valvuloplasty for mitral stenosis in middle aged and elderly patients

T R D Shaw, P Bloomfield, C M Turnbull,
A D Flapan
Department of Cardiology, Western General Hospital, Edinburgh

Percutaneous transvenous balloon dilatation of mitral valve stenosis was attempted in eight patients aged 38–74 (mean 67). In one patient with giant left atrium (dimension 14 cm) the balloon catheter could not be made to cross the septum: in seven patients balloon dilatation was carried out with a single 25 mm balloon in two, a 25 mm trefoil balloon in four, and double balloons in one. The major technical difficulty was that of achieving the optimal position of the balloon at the mitral valve orifice. Cross sectional echocardiography proved useful for positioning 3 cm length balloons, particularly in patients with a dilated left ventricle. In four patients it was necessary to advance the guide wire to the descending aorta to provide stability for the balloon to turn within the enlarged left atrium. In two symptomatic patients with moderate mitral stenosis there was only a very small reduction in resting gradient. In four patients with more severe stenosis the immediate reduction in gradient was from 12·4 to 6·4 mm Hg. Preliminary results suggest that the improvement in gradient and valve area was maintained at repeat catheterisation 2–4 months later. When positioned at the mitral orifice, balloon dilatation caused a considerable drop in aortic pressure and a slight rise in pulmonary artery pressure, but only one patient developed brief syncope. The trefoil shaped balloon did not prevent a considerable drop in systolic pressure and had the disadvantage of tending to kink, sometimes thereby preventing full deflation. Mitral valvuloplasty is an effective alternative to surgical valvotomy even in older patients.

Residual stenosis after percutaneous transluminal coronary angioplasty and its effects on left ventricular function: evidence for delayed healing at angioplasty site

Y C Najm, A D Timmis, M N Maisey, L Manuel Y Pinies, A Salinas, P V L Curry, E Sowton
Cardiac and Nuclear Medicine Departments, Guy's Hospital, London and Dept. Patologia General, Universidad del Pais Vasco, Bilbao, Spain

Percutaneous transluminal coronary angioplasty (PTCA) provides effective symptomatic relief in selected patients with angina. Nevertheless, the effects of the procedure on left ventricular function are not well defined. We prospectively studied 86 patients with single vessel coronary artery disease treated by PTCA. Thallium-201 perfusion scintigraphy and technetium-99^m left ventriculography were used to evaluate myocardial ischaemia and left ventricular ejection fraction (EF), respectively. Imaging was performed before and 3·6 (2·2) months after PTCA. Before PTCA, reversible myocardial ischaemia was present in every case and stress produced dilatation of the left ventricule with a fall in EF from a mean of 64 (6) % to 56 (7) % ($p < 0\cdot001$). After PTCA residual coronary stenosis was $\leqslant 20\%$ in 78 patients (group 1) and 20 to 50% in eight patients (group 2). Symptomatic relief and correction of reversible myocardial ischaemia were similar in both groups but group 2 showed persistent stress-induced left ventricular dilatation with a fall in EF from 65 (6) % to 56 (5) %. In group 1 the left ventricular EF response to stress tended to normalise (63% to 67%, $p < 0\cdot001$) although 30% of the group studied very early (< 6 weeks) after PTCA showed residual decompensation (61 (9) % to 52 (9) %). In this subgroup repeat studies three months later, however, showed complete correction of left ventricular function: resting EF 66%, 69% with stress, and no increase in end diastolic volume.

These date indicate that: (*a*) a residual stenosis of < 50% after PTCA is associated with a good symptomatic response but detectable left ventricular dysfunction often persists unless the residual stenosis is $\leqslant 20\%$; (*b*) the healing process at the PTCA site may delay functional improvement for up to three months.

Inferior ST segment depression during left anterior descending coronary angioplasty: inferior ischaemia or "reciprocal" change?

M S Norell, J P Lyons, J Gardener, C Layton, R Balcon
London Chest Hospital, London

During left anterior descending (LAD) coronary angioplasty inferior ST segment depression frequently occurs in association with anterior ST elevation. It is unclear whether such changes are "reciprocal" or indicate additional inferior ischaemia. Therefore, intravenous digital subtraction left ventriculography was performed before and during balloon inflation to assess ischaemia in 16 patients with single vessel coronary disease undergoing elective LAD angioplasty. A twelve lead electrocardiogram was recorded throughout. During balloon inflation eight patients (group 1) developed inferior ST segment depression (mean 2 mm, range 1–3 mm) associated with anterior ST segment elevation (mean 5 mm, range 2–9 mm). The remaining eight patients (group 2) developed either anterior ST segment elevation alone (three patients) or had no ST alteration in any lead. Left ventricular (LV) ejection fraction fell during balloon inflation in both groups (group 1, 76% to 48%; $p < 0{\cdot}001$ and group 2, 73% to 57%; $p < 0{\cdot}001$), this reduction being greater in group 1 ($p < 0{\cdot}01$). Regional shortening of the anteroapical LV segment also fell in both groups (group 1, 42% to 12%; $p < 0{\cdot}001$ and group 2, 42% to 19%; $p < 0{\cdot}001$). In contrast, regional shortening of the inferobasal LV segment did not change in either group (group 1, 30% to 37%; NS and group 2, 28% to 38%; NS), nor was there a difference between groups.

Inferior ST segment depression during LAD angioplasty, although associated with a more pronounced reduction in global LV performance, was not accompanied by a deterioration in inferobasal LV contraction. Thus such electrocardiographic change represents a reciprocal phenomenon rather than the presence of additional inferior ischaemia.

Pulsed Doppler ultrasound in the diagnosis of post-infarction ventricular septal defect

M G Cheesman, R John, N Murray, J Thomas, V J Redding
Regional Cardiac Centre, Groby Road Hospital, Leicester

Eleven patients with loud systolic murmurs that developed during the course of acute myocardial infarction were referred to the Regional Cardiac Centre. Ten had ventricular septal defects (VSDs) and one had torrential mitral regurgitation. The site of the infarct was anterior in seven and inferior in four. In all but one it was the first infarction. Mean time to transfer was 6·7 days and many patients were in a poor condition on arrival. Cross sectional echocardiography alone demonstrated the VSD in all three patients with inferior infarctions, but in only three of the seven with anterior infarcts, because the septum bulged into the right ventricle (RV). Pulsed Doppler ultrasound, however, demonstrated high velocity turbulence in the RV in all ten patients, and accurately identified the site of the defect in eight. Continuous wave Doppler identified severe mitral regurgitation in the remaining patient. Four patients were sent for operation on the basis of cross sectional and Doppler imaging alone but one died before operation. Seven patients were catheterised; single vessel disease was found in five of them, and only one graft was placed at operation. One patient in whom the operation was initially successful became breathless three months later and a loud murmur was heard. Doppler ultrasound confirmed patch dehiscence, despite essentially unchanged echocardiographic images, and correctly estimated RV pressure.

If good echocardiographic images and Doppler signals can be obtained, cardiac catheterisation is of doubtful additional benefit in these patients.

Analysis of early markers of myocardial infarction

M Ohman, Catherine Casey, W Tormey, J Horgan
Department of Cardiology, St Laurence's Hospital, Dublin, Ireland

The use of intravenous thrombolysis requires early and accurate diagnosis of myocardial infarction (MI). This is usually based on clinical assessment and ECG criteria. Serum myoglobin rises in the early phase of MI and may therefore offer additional information. We evaluated 68 patients with significant chest pain 1 hour (mean 6), who presented to the coronary care unit (CCU) within 24 hours of onset of symptoms. A 12 lead ECG was obtained and serum myoglobin, creatine kinase (CK), and CK-MB were measured within an hour. MI was confirmed in 65% of patients by use of the WHO criteria during the first 48 hours. The admission ECG was classified as ST elevation (group I), any ECG abnormality (II), and normal (III). Sixty one per cent of the MI patients were in group I, 32% in group II, and 7% in group III. Corresponding values in the non-MI group were 13%, 71%, and 17% respectively. Mean (SD) total CK and CK-MB activities (144 (187) IU/l and 17 (24) IU/l respectively) in the MI group were significantly higher than those in the non-MI group (49 (37) ($p < 0{\cdot}02$) and 6 (4) ($p < 0{\cdot}05$) respectively). Serum myoglobin was also higher in the MI group (188 (139) μg/l) than in the non-MI group (46 (49) μg/l ($p < 0{\cdot}001$)). There was a good correlation between a radioimmunoassay and a rapid latex agglutination test ($p < 0{\cdot}001$) that gave a result within 10 minutes for serum myoglobin. By stepwise analysis of the ECG and myoglobin, using group I alone, and group II and III ECG with an abnormal myoglobin (> 90 μg/l) we could identify 82% of patients who would develop a MI on follow up with 17% false positives.

These data suggest that analysis of ECG and serum myoglobin (measured by a rapid latex kit) as early markers of MI could identify the majority of patients who develop MI within an hour of admission to a CCU. This simple and fast stepwise analysis would be useful in identifying patients for intravenous thrombolytic treatment.

β blockers and the hypokalaemia associated with acute chest pain

C Wong, E Simpson, C Robertson, J C Rodger
Departments of Medicine and Biochemistry, Monklands District General Hospital, Airdrie and Department of Mathematics, Strathclyde University

Plasma potassium was measured on admission in 1234 patients who presented with acute ischaemic chest pain. 195 of the patients were on β blockers before admission. Comparison of the potassium concentrations of patients admitted early (within 4 hours of onset of symptoms) with those admitted later (4 to 18 hours) showed that in patients not pretreated with β blockers there was a transient fall in plasma potassium (difference in group mean 0·13 mmol/l, $p < 0.001$). This produced an early transient increase in the occurrence of hypokalaemia (difference in group mean 11%, $p < 0.01$). Neither the fall in potassium nor the increase in hypokalaemia was seen in patients who had been on β blockers before admission. Further, when only patients admitted within 4 hours of onset of symptoms were considered, pretreatment with β blockers was shown to be associated with a higher mean plasma potassium (difference in group mean 0·14 mmol/l, $p < 0.01$) and a lower frequency of hypokalaemia (difference in group mean 16%, $p < 0.01$) than those on no drug treatment. Non-selective β blockers were found to be more effective than cardioselective agents in maintaining plasma potassium concentrations.

These findings suggest a mechanism for the beneficial effects of β blockers on morbidity and mortality in acute myocardial infarction.

Exertional ventricular tachycardia and myocardial ischaemia after coronary artery surgery

C E Handler, N Hamouratidis, A Pipilis, E Sowton, P Deverall, A Yates
Guy's Hospital, London

Coronary artery bypass grafting (CABG) improves angina but its effect on exercise induced ventricular arrhythmias is unclear. We examined this issue in 54 male patients who underwent symptom limited treadmill exercise testing one day before and 10 days, one month, and six months after CABG. Exercise haemodynamic function and tolerance increased progressively after CABG. Values at six months were: maximal heart rate 118 to 151 beats/minute ($p < 0.001$); rate-pressure product 16·6 to 27·0 × 1000 ($p < 0.001$); and exercise duration 11·9 to 16 5 minutes ($p < 0.0001$). The frequency of angina (67% to 2% ($p < 0.001$)) and ST segment depression (71% to 20% ($p < 0.001$)) both decreased significantly early after CABG, but in 11 patients ST segment depression developed at six months. The frequency of ventricular arrhythmias recorded at rest, during exercise, and after exercise increased significantly after CABG; 85% of the patients had an exertional ventricular arrhythmia at one month. The occurrence of complex ventricular arrhythmias (couplets or ventricular tachycardia) also increased postoperatively; 18 patients had unsustained exertional ventricular tachycardia at one month. The occurrence of ventricular arrhythmias appeared unrelated to previous myocardial infarction, the extent of coronary artery disease, or the number of grafts inserted.

We conclude that although CABG improves myocardial ischaemia and exercise tolerance, serious ventricular arrhythmia appears to be more common after CABG and unrelated to myocardial ischaemia. This observation may partly explain the reported improvement in symptoms but largely unchanged prognosis in certain groups of patients after CABG.

Long term clinical follow up of patients after coronary surgery and assessment of the benefits of postoperative aspirin and dipyridamole

A H Gershlick, R Balcon
The London Chest Hospital, London

A trial of aspirin and dipyridamole (Persantin) after coronary bypass grafting was undertaken between 1978 and 1982. The 320 patients entered have now been further assessed a mean of 6·6 years after operation. Those in the active group took aspirin (300 mg three times a day) and dipyridamole (75 mg three times a day) for a mean 25 months. There were 33 deaths during the follow up and 25 (7·8%) were due to cardiac causes. Fifteen of the 25 cardiac deaths occurred in patients with abnormal preoperative ventriculograms. Thirteen cardiac deaths occurred in the active group and 12 in the placebo group. Five patients refused follow up. Of the 282 patients thus available for review, 250 attended as outpatients and were assessed with a detailed questionnaire and exercise stress test. One hundred and twenty two had been given active treatment and 128 had been given placebo. Ninety four of the 250 patients complained of angina (49 active, 45 placebo), which had developed a mean 31 months after operation, and 52 of these (28 active, 24 placebo) had abnormal exercise tests. Sixteen patients (6 active, 10 placebo (NS)) required repeat angiography for recurrent symptoms. Eight of the 12 patients (4 active, 8 placebo (NS)) who have had a further operation continue to be symptomatic. Of the nine patients who sustained myocardial infarction during follow up, seven were in the active group. Only nine of the 23 patients with properative hyperlipidaemia and 23 of 66 postoperative smokers were among the 94 patients with recurrence of symptoms. Thus 6·6 years after vein grafting 156 (62·4%) of 250 patients were symptom free and 104 (41 6%) were in full time work.

Administration of aspirin and dipyridamole for a mean 25 months after coronary bypass grafting does not confer long term clinical benefit.

Neuropsychological sequelae of bypass twelve months after coronary artery surgery

G Venn, L Klinger, P Smith, M Harrison,
S P Newman, T Treasure
Middlesex Hospital and Medical School, London

We have reported to the society the short term (8 week) cerebral consequences of coronary artery bypass surgery (CABS) compared with a group undergoing major vascular surgery. We have now completed one year assessments on a cohort of 66 CABS patients previously evaluated before operation and eight days and eight weeks after operation. Ten tests, designed to be sensitive to minor diffuse cortical impairment, were administered on each of these occasions. Neuropsychological deficit was considered to be present when the postoperative performance showed a deterioration by at least one standard deviation (SD) from the patient's preoperative measure in two or more tests. Seventy three per cent (70% confidence interval, 66%–79%) showed a deficit at eight days, improving to 38% (70% confidence interval, 31%–45%). There was no further improvement at 12 months when 35% (70% confidence interval, 28%–42%) still showed impairment. Neuropsychological deficit was strongly associated with age (mean (SD) 59 (6·6) *vs* 53 (7 8) years; Mann-Whitney $U = 697$, $p < 0{\cdot}01$), longer bypass time (94 (22) *vs* 83 (27) min; $U = 623$, $p < 0{\cdot}05$), and with operation time (263 (58) *vs* 236 (61) min; $U = 644$ 5, $p < 0{\cdot}05$).

These findings indicate that the cortical effects of CABS are related to the magnitude of surgery and the age of the patient and persist for at least 12 months after operation.

Determinants of patient status ten years after coronary bypass grafting for angina

J Al Khatib, A G Mitchell, M H Yacoub
Harefield Hospital, Harefield, Middlesex

Between October 1969 and December 1975, 428 patients underwent isolated coronary artery bypass grafting (CABG) for angina at Harefield Hospital. Thirty six patients were lost to follow up, leaving 392 (92%) for follow up over a minimum period of 10 years (mean 11 5 years). Perioperative mortality was 3·6% and reoperation before 10 years was performed in 15 (3·8%) patients. Five and 10 year survival rates were 85% and 67% respectively with an annual mortality rate of 2·5% for the first five years and 3·0% between five and 10 years. We studied the influence of the patient's age, sex, coronary risk factors, previous infarction, coronary anatomy, left ventricular function, use of internal mammary artery graft, endarterectomy, perioperative infarction, and graft patency at one and five years after operation on the survival at ten years. Late survival was reduced by age >60, hypertension, multivessel disease, and impaired left ventricular function, and improved by full graft patency and possibly by use of an internal mammary artery graft. Of the 273 survivors at 10 years, 100 (38%) were symptom free without a cardiovascular event (that is myocardial infarction or reoperation). One hundred and twenty (46%) had varying degrees of angina, 59 (22%) had clinical evidence of heart failure, and 31 (11·8%) had late myocardial infarction. Of the possible determinants of symptomatic status studied, hypertension increased the incidence of angina, and poor left ventricular function increased the incidence of heart failure. Full graft patency increased the proportion of symptom free survivors.

It is hoped that these data will be useful in predicting and optimising late results of CABG.

Functional assessment of internal mammary artery grafts

Ann C Tweddel, W Martin, I McGhie,
J C S Pollock, I Hutton

Departments of Medical Cardiology and Cardiac Surgery, Royal Infirmary, Glasgow

Internal mammary artery grafts to the left anterior descending coronary artery have been shown to have favourable patency rates, but the ability of these grafts to respond to stress is less clear. A group of 15 symptom free patients with patent internal mammary artery grafts at a mean of two years were investigated. Regional myocardial nutrient flow was assessed from the clearance of xenon-133 by a gamma camera fitted with a specially designed high sensitivity biplane collimator, which allowed simultaneous acquisition of 30° and 70° left anterior oblique projections. After direct injection into the graft, left ventricular flow was measured at rest, during atrial pacing at 100 beats/minute, and during atrial pacing at a rate similar to that during maximal exercise (mean 124 beats/minute). In six patients the diameter of the grafted vessel was smaller than the internal mammary artery graft and in these patients mean resting myocardial flow was 45·7 (5·0) ml/100 g/min, falling with atrial pacing at 100 beats/minute to 36·9 (6·4) ml/100 g/min ($p < 0.05$) and falling further to 31·2 (6·2) ml/100 g/min ($p < 0.02$) at the higher pacing rate. In nine patients the diameter of the grafted vessel was similar or larger than that of the graft. Mean resting flow was 52·8 (3·9) ml/100 g/min and was maintained with pacing at 100 beats/minute (53·3 (8·7) ml/100 g/min (NS)), and increased on pacing at 124 beats/minute to 58·5 (5·8) ml/100 g/min ($p < 0.05$).

These results suggest that despite the favourable angiographic appearance the capacity of an internal mammary artery graft to respond to stress is dependent on the interface of the implant to the grafted vessel.

Low energy level internal defibrillation during cardiopulmonary bypass

W B Pugsley, T Baldwin, T Treasure,
M F Sturridge
The Middlesex Hospital, London

High energy electrical shocks damage the myocardium. Nevertheless, it is still common practice to use 20–30 J shocks to defibrillate hearts during cardiopulmonary bypass: some defibrillators cannot be set to deliver less than 10 J. We have modified a standard Albury Lifeguard Defibrillator to deliver energy in small increments starting at 1 J and proceeding to 2, 4, 6, 8, 9, 12, 15, 20, and 30 J. During the period 1983–85, 168 patients (118 M and 50 F; median age 58, range 4–77) required defibrillation on cardiopulmonary bypass. They were successfully defibrillated with the modified defibrillator. Eighty eight (52·3%) patients underwent coronary artery grafting; 59 (35·1%) had valves replaced (22 aortic, 33 mitral, and 4 double valves); and 12 of the remaining 21 patients had correction of congenital defects.

Seventy eight (46%) patients were defibrillated with 2 J or less. In 139 (82·7%) patients defibrillation was effected with 4 J or less. Only four patients required >10 J to defibrillate their heart.

We recommend the use of low energy defibrillation as a means of preventing electrical damage to the myocardium.

The role of peroperative hypocapnia in the aetiology of neurological deficit after cardiopulmonary bypass surgery

M Nevin, S Adams, A C F Colchester, J R P Pepper
Department of Cardiothoracic Surgery, St George's Hospital, London

Thirty patients undergoing coronary artery bypass surgery had a detailed preoperative and postoperative ophthalmological and neuropsychological assessment. Anaesthetic and surgical protocols were standardised, although ventilatory variables were left to the discretion of the anaesthetist and as such closely conformed to accepted clinical practice. A continuous recording of mean arterial pressure, jugular venous pressure, and cerebral perfusion pressure was obtained peroperatively. Blood gas analysis was performed at regular intervals peroperatively. Although none of the patients complained of visual symptoms after operation seven (28%) were found to have ophthalmological signs highly suggestive of ocular hypoperfusion. No intraluminal emboli or evidence of branch vessel embolisation was noted. Examination of the results of the peroperative monitoring showed that the group showing positive postoperative ophthalmological signs had: (*a*) significantly lower arterial carbon dioxide ($p < 0.001$) and oxygen ($p < 0.01$) tensions at the onset of cardiopulmonary bypass (CPB); (*b*) a significantly greater rise in both $PaCO_2$ ($p < 0.01$), and jugular venous pressure ($p < 0.01$) at the onset of CPB; (*c*) a significantly lower mean cerebral perfusion pressure ($p < 0.01$) during the first ten minutes of CPB, a period not maximally covered by the cerebral protecting capabilities of hypothermia. In addition they showed significantly a greater postoperative neuropsychological deficit (80%) than the group who showed no new ophthalmological signs (40%).

Right and left ventricular function after anatomical correction and the Mustard and Senning operations for transposition of the great arteries

R P Martin, J A Ettedgui, S A Qureshi, E J Baker,
O D H Jones, M H Maisey, A K Yates, P B Deverall,
R Radley-Smith, M Tynan, M H Yacoub
Departments of Paediatric Cardiology, Guy's
Hospital, London and Harefield Hospital,
Harefield, Middlesex

After definitive surgery for transposition of the great arteries (TGA) late morbidity and mortality can be associated with ventricular dysfunction. We examined right and left ventricular function by first pass and equilibrium gated nuclear angiography in 21 patients after anatomical correction of TGA and in 21 patients after intra-atrial repair of TGA by the Mustard (11 patients) and Senning (10 patients) operations. The mean age of the patients after anatomical correction was 51·8 (range 17–85) months and the studies were performed a mean of 47·1 (range 17–78) months after operation. Thirteen patients had undergone primary correction (nine as a neonate and four with ventricular septal defect) and eight had preliminary pulmonary artery banding as part of a two stage repair. The mean age of the patients after intra-atrial repair of TGA was 82·8 (range 13–228) months and studies were performed a mean of 67 4 (range 3–187) months after operation. After injection of technetium-99m labelled autologous erythrocytes, the right ventricular ejection fraction (RVEF) was determined from the first pass study in the anterior projection and the left ventricular ejection fraction (LVEF) from an equilibrium study in the left anterior oblique projection. After anatomical correction the mean RVEF was 57·9% (11·99) and after intra-atrial repair it was 51·1% (10·54). After anatomical correction the mean LVEF was 58·2% (8·68) and after intra-atrial repair it was 57·7% (10·99). The difference in systemic ventricular ejection fraction between the two groups is not statistically significant ($0{\cdot}05 < p < 0{\cdot}1$); however, moderately severe ventricular dysfunction ($\mathrm{EF} \leqslant 30\%$) was only seen after intra-atrial repair (two patients).

Total anomalous pulmonary venous drainage: a seventeen year surgical experience

R K Lamb, S A Qureshi, J L Wilkinson, R Arnold,
D I Hamilton
Royal Liverpool Children's Hospital, Liverpool

Between 1968 and 1985, 80 children underwent repair of total anomalous pulmonary venous drainage (TAPVD). There were 47 boys and 33 girls (aged from 3 days to 16 years, mean 7 7 months). Seventy (88%) of the children were < a year old at operation. Fifty eight (73%) weighed < 5 kg (range 1·6–42 kg, mean 4·9 kg). Forty five (56%) children had supracardiac, 14 (18%) cardiac, 15 (19%) infracardiac, and six (7%) mixed TAPVD. Pulmonary venous obstruction was present in 27 (34%). The pulmonary artery (PA) peak systolic pressure ranged from 24 to 140 mm Hg (mean 62) and the RV:LV peak systolic pressure ratio from 0·38 to 1 8 (mean 0 88). There were 14 (17 5%) early deaths, of which seven (15%) occurred in the supracardiac, two (14%) in the cardiac, four (26%) in the infracardiac, and one (16%) in the mixed TAPVD groups. During a mean follow up of 65 months (range 6–189 months) there were six (7·5%) late deaths. Multivariate analysis showed no significant influence of sex, age at operation, weight at operation, anatomical type, the presence of pulmonary venous obstruction, or the technique of operation. Postoperative pulmonary venous obstruction occurred in five (6%) patients between six weeks and nine months after operation. All five died, three after reoperation. The surviving patients were all symptom free.

Early repair of TAPVD is feasible irrespective of age and gives excellent long term results. The recurrence of pulmonary venous obstruction after operation, however, is an important adverse factor influencing the late results.

Results of surgery for interrupted aortic arch in infancy: a multivariate and logistic analysis

S A Qureshi, B Maruszewski, Roxane McKay,
D I Hamilton
Royal Liverpool Children's Hospital, Liverpool

Between 1971 and 1986, surgery was performed in 23 infants with interrupted aortic arch (IAA) (11 boys and 12 girls; weight 1 7–4·2 kg (mean (SD); 3 1 (0·63); age 2–90 days (13 (18·7)). Arch interruption was type A in four (17%) patients, type B in

17 (74%), and type C in 2 (9%). Associated cardiac lesions included transposition of the great arteries (2), truncus arteriosus (1), tricuspid atresia (1), double inlet ventricle (1), aortopulmonary window (1), and ventricular septal defect (VSD) (23). The arch was reconstructed with a prosthetic conduit in 12 patients, by direct anastomosis in six, with the left subclavian artery in three, and with the ductus arteriosus in two. Four patients had simultaneous closure of a VSD; pulmonary artery banding was performed in 15 of the remaining 19. Of the 13 (57%) operative deaths, five occurred in patients with complex cardiac defects and three when single stage repair was attempted. Survival after a palliative procedure in patients with VSD was 62% and six of these patients subsequently underwent pulmonary artery debanding and VSD closure with one death. χ_2 and t tests of 13 variables showed that only the year and the type of operation were significantly associated with improved survival. Multiple logistic regression identified male sex, preoperative prostaglandin infusion, absence of cardiac catheterisation, and older age at operation as favourable predictors.

The two stage repair with interposition of a conduit from ascending to descending aorta now offers good palliation for infants with IAA and VSD.

The changing role of duplex scanning in the preoperative evaluation of congenital heart disease

G R Sutherland, Anna Colli, B R Keeton,
J L Monro, D F Shore
Wessex Regional Cardiac Centre, Southampton General Hospital, Southampton

Previous studies on the usefulness of ultrasound in the preoperative assessment of congenital heart disease have been restricted to small selected patient populations. The potential benefits and problems inherent in surgical referral based solely on clinical or ultrasound studies or both have not been defined in terms of a total paediatric cardiology practice. Furthermore, no study has investigated what additional benefits may have accrued from the introduction of integrated Doppler echocardiography. To this end we reviewed the total population (4289 new referrals) of a regional paediatric cardiology unit over a seven year period (1980–86). 1094 children underwent cardiac surgery (669 bypass, 425 closed), 240 of whom had not had preoperative catheterisation (10% bypass, 41% closed). The overall catheter:operation ratio (C:O ratio) fell progressively from 1:1 in 1980 (both bypass and closed) to 0·42:1 in 1986 (bypass 0 76:1, closed 0·3:1). Further analysis of three main groups (*a*) neonates, (*b*) infants, and (*c*) children aged 1–14 years indicated that the main impact had been on the neonatal and infant groups where cardiac morphology was the main determinant of operation without catheterisation (1986—neonatal C:O ratio, bypass = 0·27:1, closed = 0·0:1; infant C:O ratio, bypass = 0·76:1, closed = 0·42:1). Statistical analysis confirmed that Doppler echocardiography increased the non-invasive referral rates in all three groups and had its greatest effect in defining outflow tract gradients. During the study there were three important ultrasound misdiagnoses (1 3% total) with no resultant surgical mortality, a level of inaccuracy comparable to that in the catheterised group (0·9% total).

With the introduction of Doppler echocardiography non-invasive assessment is increasingly a practical alternative to preoperative catheterisation in well defined subsets of a total paediatric cardiology practice.

Transcatheter occlusion of persistent ductus arteriosus

M Tynan, R P Martin, J A Ettedgui, J S Reidy
Paediatric Cardiology Department, Guy's Hospital, London

Transcatheter occlusion of persistent ductus arteriosus is an attractive alternative to operation. We have successfully implanted occlusion devices in 10 patients aged 1–63 years using Rashkind (USCI) transcatheter occlusion system. The percutaneous approach was used in all—via the femoral vein in nine and the femoral artery in one. From the vein a long sheath was advanced to the aortic opening of the ductus arteriosus whereas from the arterial approach the sheath was advanced to the pulmonary artery opening. The delivery system and occluding device were then advanced, and by manipulation of the delivery system and sheath the device was positioned so that it straddled the pulmonary opening of the ductus arteriosus. It was then released. The PDA was occluded by a 12 mm device (8 French delivery system) in six patients and by a 17 mm device (11 French delivery system) in four patients. In one patient the occluding device was incorrectly positioned and was released into the aorta. It lodged at the aortic bifurcation from where it was retrieved with an ureteric basket catheter and removed via a right femoral arteriotomy. Six weeks later, at the patient's request, successful transcatheter occlusion was performed. Doppler evaluation 24 to 48 hours after occlusion showed absence of ductal flow in eight and reduced ductal flow in two patients.

Successful transcatheter occlusion of a ductus arteriosus can be achieved in a wide age range of patients. Complications in relation to the accurate placement of the device were encountered in the learning phase.

Balloon angioplasty as first-line treatment for aortic coarctation

I Peart, C Wren, H H Bain, S Hunter
Freeman Hospital, Newcastle upon Tyne

Although balloon angioplasty is widely used for the treatment of postoperative recoarctation of the aorta, its role as first-line treatment for native coarctation has yet to be established. We present our results with balloon dilatation of native coarctation in 13 patients aged 1–19 (mean 11) years. Nine (69%) were hypertensive on presentation. Under general anaesthetic the systolic pressure gradient across the coarctation was 24–50 (mean 30) mm Hg. The aortic diameter above the coarctation was 6–23 (mean 14) mm and at the coarctation site it was 4–9 (mean 6) mm. The size of balloon catheter used was based on the diameter of the distal aortic arch. Meditech balloon catheters, 8–18 mm in diameter, were inflated 1–4 (mean 2·1) times at 60–110 psi. The ratio of balloon:coarctation diameter in individual patients was 2·0–4·5 (mean 2·7). After angioplasty the systolic pressure gradient fell to 0–20 (mean 6) mm Hg ($p<0·01$) and the coarctation diameter increased to 7–20 (mean 12) mm ($p<0·01$). Only one patient developed diffuse dilatation at the coarctation site (balloon:coarctation ratio of 4·5). At follow up all patients were normotensive (only one on treatment). Reinvestigation at 6–16 (mean 12) months in 12 patients demonstrated residual gradients of 0–24 (5) mm Hg; one of these patients underwent successful redilatation.

Balloon angioplasty is effective in relieving native coarctation. The frequency of aortic dilatation at the site of the coarctation is small and may be related to balloon size. Our early experience with balloon angioplasty for native coarctation is encouraging. Its adoption as first-line treatment will depend on long term results and further experience.

Elective day case cardiac catheterisation: Judkins' technique

K G Oldroyd, K V Phadke, Rosalind Phillips, P Carson, M Clarke, J A S Davis
North Staffordshire Hospital Centre, Stoke-on-Trent

Judkins' catheterisation is frequently performed as an inpatient procedure for fear of haemorrhage or other complications. A policy of day case catheterisation has been gradually adopted in this centre. During the 33 month period of this survey of 972 left heart studies (96% including coronary arteriography), including cases of recently unstable angina, 719 (74%) were performed electively as day cases; 43% had left main or triple vessel disease. Patients attended the cardiac department one hour before the procedure, which was performed without premedication using a French 7 or 8 sheath; patients taking warfarin were instructed to omit the treatment the day before the study. After catheterisation patients were observed in the day room of the cardiology ward for a minimum of four hours. 675 (94%) had uncomplicated procedures. There were two deaths (0·3%). 44 (6%) patients had to be admitted: eight with prolonged chest pain, seven with significant puncture site haemorrhage, six with acute infarction, and three with major vascular complications. Puncture site haemorrhage occurred within four hours except in one case (6 hours); it did not occur in any patient after discharge. The incidence of haemorrhage was unrelated to sheath size but was slightly more common in patients who had been receiving warfarin (4% *vs* 1%).

Day case femoral cardiac catheterisation can be performed with an acceptably low complication rate. Compared with a policy of admission there is less disruption of the catheterisation service by lack of beds; also a considerable cost saving and greater convenience for patients.

Provision of pre-hospital coronary care by a taxi service

G Main, G P McNeill
Ninewells Hospital and Medical School, Dundee

A mobile coronary care unit staffed and driven by a doctor and nurse was started in Dundee in 1977. During 1985 Tayside Health Board considered discontinuing the service because the van had been repeatedly involved in road traffic accidents. Since 6 January 1986 the unit has been conveyed by a local taxi firm. Patients are transferred to hospital by conventional ambulance. We have reviewed our initial 10 month experience of this novel service. There have been 458 calls, mean cost £5·33 each, compared with approximately £8·00 for the previous doctor driven service in 1984. The mean distance travelled was four miles. 51% of requests were from general practitioners, 22% from ambulance-men, 8% from GP receptionists, 4% from other hospitals, and 15% directly from patients. The median time between requests for service and arrival at the patient was 14 minutes compared with 11 minutes previously. Drug treatment was given in 66% of calls; 65% of patients required hospital admission, 38% to a coronary care unit. During the first year of this service advanced cardiopulmonary resuscitation was attempted out of hospital on 18 occasions; however, only three cardiac arrests occurred in the presence of the team; two of these patients survived and remained well. There have been no road accidents.

The taxi based mobile coronary care unit can provide a low cost safe method of transporting a mobile unit team into the community.

Type A behaviour pattern in patients with coronary artery disease

Leisa J Freeman, P G F Nixon
Charing Cross Hospital, London

Possession of the type A behaviour pattern (TABP) is considered to be a risk factor in patients with coronary artery disease and may exert its effect by excessive stimulation of the sympathoadrenal medullary system. Additionally, type A subjects may perceive life events as more stressful than type B subjects. The frequency of the TABP in 30 patients undergoing routine angiography was studied by the Gough adjective check list and Thurston Activity schedule (these reflect time, pressure, and speed at which activities are undertaken). Forty eight hour ambulatory ST Holter monitoring was performed with concomitant collection of urinary catecholamine (nonadrenaline and adrenaline) during a stressful period in the patients lives and at a later date. The effect of possession of the TABP on the occurrence of myocardial ischaemia during daily life on these two separate occasions was studied. Patients kept a comprehensive diary of episodes of chest pain and emotional upset. Scores consistent with previously documented interview assessment of type A1 behaviour pattern were obtained in 12 (Gough) and 14 (Thurston) patients. There was good correlation between the questionnaires. Type A patients experienced many more episodes of painful myocardial ischaemia during the stressful period of monitoring than at the later date ($p<0.02$). They also had a higher excretion of adrenaline ($p<0.03$) at this time and reported more episodes of emotional upset compared with the later time ($p<0.02$). There was no effect on the frequency of asymptomatic ischaemia.

Apolipoprotein AI/CIII/AIV DNA sequence markers, hyperlipoproteinaemia, and coronary artery disease in Scotland

W H Price, A H Kitchin, H Tunstall-Pedoe, T R D Shaw, J C Rodger
MRC Cytogenetics Unit and Department of Medicine, Western General Hospital, Edinburgh, Cardiovascular Epidemiology Research Unit, Ninewells Hospital, Dundee, and Monklands District General Hospital, Airdrie

It is well recognised that in coronary heart disease (CHD) a family history is an important risk factor. Occasionally it is due to a mendelian genetic disorder such as familial hypercholesterolaemia but in most instances it is attributed to a combination of multiple genetic and common environmental factors. With recombinant DNA technology it is now possible to assess and analyse the genetic contribution in several diseases and already several reports suggest that variants of the genes that code for apolipoproteins (apo) are implicated in CHD. Using standard techniques we have identified allelic variants at five polymorphic DNA endonuclease restriction sites in the apoAI/CIII/AIV gene cluster and have determined their frequencies (*a*) in two Scottish populations ($n=224$ and 130) with different standardised CHD mortality ratios (81 and 138), (*b*) in survivors of myocardial infarction in two coronary care units ($n=62$ and 52), and (*c*) in patients assessed by coronary angiography ($n=100$). Our results so far show a significant association between the frequency of allelic variants at a PstI site flanking the 3′ end of the apoAI gene and hyperlipidaemia (total cholesterol 7·5 mmol/l; triglycerides 2·1 mmol/l; $p<0.005$), and with CHD before the age of 55 years ($p<0.01$).

The findings are consistent with linkage disequilibrium between the apoAI/CIII/AIV gene marker and a gene or genes which confer predisposition to CHD in the Scottish population.

Neuropeptide Y causes myocardial ischaemia in man by small vessel constriction

J Clarke, G Davies, R Kerwin, D Hackett, S Larkin, D Dawbarn, Y Lee, S Bloom, M Yacoub, A Maseri
Royal Postgraduate Medical School, London

Peptidergic nerves appear to have a physiological role in cardiovascular regulation. Neuropeptide Y (NPY) is found in abundance in epicardial human coronary arteries in relation to noradrenergic nerves and is a potent constrictor of coronary arteries in isolated rabbit heart. We studied six patients with chest pain but no evidence of variant angina. Provocation tests including exercise, hyperventilation, ergometrine, and histamine were negative. All patients had either normal coronary arteries or only minimal wall irregularities, although one had evidence of previous myocardial infarction. During ECG monitoring, coronary arteriography was performed before and after control intracoronary infusions of 1% albumin in physiological saline and was repeated after five-minute intracoronary infusions of 0·2, 0·6, and 1·0 pmol/kg/min of NPY into the left (five patients) or right (1 patient) coronary artery. The epicardial vessel diameter was measured by computerised arterial analysis (CAAS-Pie Data Medical). Anginal pain with ST segment elevation occurred in 3 patients (two patients at 0·2 and 1 patient at 1·0 pmol/kg min). This was associated with interruption of flow in the infused artery as indicated by lack of progression of contrast. There was a slow return to a normal flow pattern after 2 mg of intracoronary isosorbide dinitrate. In the early phase of recovery when ischaemia had not completely resolved, lack of progression of contrast was still evident in the distal segment of the artery but there was no evidence in the proximal segment of focal constriction of the type seen in variant angina.

NPY produces myocardial ischaemia without epicardial vessel changes and therefore is a constrictor of small coronary vessels.

The influence of short term or long term aspirin administration after experimental vein graft insertion

Denise Syndercombe Court, J C Chalmers, C T Lewis, P G Mills
The London Hospital, London

We have used a rabbit model of autogenous vein grafting to investigate the effect on graft intimal thickness of 40 mg/kg aspirin given daily for three days or for 28 days after insertion of a jugular vein graft into the carotid artery. Three groups of eight rabbits were grafted: untreated controls, three day treated, and 28 day treated. All animals were killed at 28 days (though one animal in the 28 day treated group died during the experimental period). Grafts were removed, fixed at pressure, and cut into seven cylindrical lengths. Intimal thickness was measured under microscopy with an Apple graphics tablet from elastin-van Gieson stained sections. A mean of 299 measurements was made on each section and the average intimal thickness was calculated for each graft. The mean thickness (μm (SEM)) for each group was: control 65·41 (8·23); three day treated 76·03 (7·37); 28 day treated 147·13 (79·60). Nonparametic analysis of the data indicated that, while there was no significant difference between the three day and 28 day treated groups, it can be stated with 95% confidence that the presence of aspirin was consistent with a reduction of up to 19% or an increase of up to 108% in intimal thickening.

While aspirin has proven beneficial effects in reducing the incidence of early postoperative thrombosis, its potential, in a high dose, to produce greater intimal thickening, which may affect the long term survival of the graft, must also be considered.

Coronary anatomy and collateral vessels during evolving acute myocardial infarction

D Hackett, G Davies, S Chierchia, A Maseri
Royal Postgraduate Medical School, Hammersmith Hospital, London

We investigated the relation of symptoms and coronary arteriographic findings in 65 consecutive patients aged 27–78 years presenting with acute myocardial infarction. Coronary arteriography was performed before administration of thrombolytic treatment at a mean of 4·0 (range 1·1–7·9) hours after the onset of continuous chest pain.

Twenty three patients gave a history of chronic stable angina pectoris and 21 of recent onset unstable angina; 21 had no history of pain before infarction. The infarct related coronary artery was occluded in 58 patients and patent with a severe stenosis in seven; in 37 it was the only coronary obstruction present. In 45 patients collateral vessels were seen filling the infarct related coronary artery, but they were present with partial or complete filling of the infarct related artery in 20. There were no significant differences in the frequency of collateral filling of the infarct related artery between those patients with (seven of 23) or without (13 of 32) chronic angina. Multiple vessel obstruction, particularly three vessel disease, was more common in patients with chronic stable angina ($p < 0·05$).

Patients with acute myocardial infarction most commonly have single vessel disease. Collateral vessels rarely fill the infarct related artery during the early phase of infarct evolution and are no more frequent in patients with preceding chronic angina.

Pulmonary embolectomy: indications and results

H H Gray, J M Morgan, M Paneth, G A H Miller
Brompton Hospital, London

Between 1964 and 1986 139 patients with acute massive pulmonary embolus (AMPE) were admitted to this hospital. Before 1968 pulmonary embolectomy was the only specific treatment available and was performed on 30 patients, with a mortality of 33·3%. Although the introduction of thrombolytic treatment as an alternative treatment reduced the annual number of pulmonary embolectomies this operation was still required in 41 of 109 patients admitted with AMPE (37 6%) either because the patient was too sick to allow a trial of thrombolytic treatment (5 cases) or because there was a specific contraindication to thrombolysis (30 cases) or operation was considered to be the treatment of choice (4 cases). Two patients started on streptokinase but later required emergency embolectomy. Thus over the whole period 71 pulmonary embolectomies were performed: of these, 21 (29·6%) patients died. Sixteen of those who died had required preoperative external cardiac massage (ECM), indicating the severity of their haemodynamic impairment. Three of these 16 died on bypass, nine died within four weeks with severe neurological damage, three died in the first postoperative week of circulatory or multisystem failure, and one patient died at five weeks with carcinomatosis. Of the five patients who died without having had preoperative ECM one died on bypass, one died of pleural and one of gastrointestinal bleeding, one patient died within 24 hours of persistent hypotension, and one at six days with massive venous occlusion requiring thrombectomy. An additional patient died five months after operation with a further pulmonary embolus. Fifty (70 4%) of the 71 patients survived to leave hospital. One underwent a period of haemodialysis and then made a full recovery, three had moderate neurological deficits which were thought to have been present preoperatively, and one developed a hemiplegia perioperatively, probably caused by paradoxical embolus through a patent foramen ovale. The remaining survivors ($n = 45$) recovered completely. Out of the total group of 71 patients undergoing pulmonary embolectomy 25 had required preoperative ECM. In the latter patients the mortality was 63·6% compared with 12·2% in patients who had not required ECM.

We conclude that pulmonary embolectomy is still an important and effective form of treatment for AMPE.

Sudden death in hypertension: a possible mechanism

J M McLenachan, E Henderson, G B Lindop, H J Dargie
The Cardiac Department, Western Infirmary, Glasgow

Sudden death is common in hypertensive patients with electrocardiographic left ventricular hypertrophy (ECG LVH) and is often attributed to myocardial infarction secondary to otherwise silent coronary artery disease. In other forms of cardiac hypertrophy, however, primary ventricular arrhythmias occur frequently and are predictive of subsequent sudden death. We investigated the occurrence of ventricular arrhythmias by 48 hour ambulatory ECG monitoring and their relation to coronary artery disease in hypertensive patients with and without ECG LVH and in a normotensive control group. Ventricular tachycardia (VT) ($\geqslant 3$ ventricular impulses at a rate >120 per minute) occurred in 1/50 (2%) control subjects, 4/50 (8%) hypertensive patients without LVH, and 14/50 (28%) hypertensive patients with LVH ($p < 0\ 01$ *vs* controls, $p < 0{\cdot}05$ *vs* hypertensives without LVH). Coronary arteriography in 16 of those with VT demonstrated normal coronary arteries in nine (56%) and single vessel disease in four (25%). Left ventricular endomyocardial biopsy specimens from those patients with VT were analysed by point counting and compared with biopsy specimens from patients with a similar degree of LVH but without VT on ambulatory monitoring. Volume fractions of interstitium and of fibrosis were 19 (4)% and 13 (3)% respectively for those with VT and 3 (1)% ($p < 0{\cdot}001$) and 2 (1)% ($p < 0{\cdot}001$) for those without.

Ventricular arrhythmias occur commonly in hypertensive patients with left ventricular hypertrophy; their occurrence cannot be attributed solely to coexistent coronary artery disease, but is related to myocardial complications of left ventricular hypertrophy, including myocardial fibrosis. They may contribute to the high frequency of sudden death in hypertensive patients.

Aortic valve replacement with and without myocardial revascularisation in patients with coronary artery disease

P M Schofield, M Jones, H Moussalli, A K Deiraniya, R A M Lawson, N H Brooks
Regional Cardiac Unit, Wythenshawe Hospital, Manchester

To assess the role of myocardial revascularisation in patients with combined aortic valve disease (AVD) and coronary artery disease (CAD) early and late outcome were determined in 630 patients who underwent aortic valve replacement between 1974 and 1982. Three groups of patients were identified. Group I (506 patients) did not have significant CAD (>50% reduction of intraluminal diameter of a major coronary artery), group II (69 patients) had CAD and underwent coronary artery bypass grafting, and group III (55 patients) had CAD but did not undergo myocardial revascularisation. Patients in group II had more severe CAD than those in group III: 10 had left main stem stenosis, 17 had three vessel disease, 19 had two vessel disease, and 23 had single vessel disease, compared with 2 patients, 2 patients, 16 patients, and 35 patients respectively in group III. The overall early mortality (within 30 days of operation) was 6% for group I, 13% for group II, and 16% for group III, although operative mortality was lower in patients operated on more recently (3%, 8%, and 13% respectively). The three year survival of patients in group I (83%) was significantly higher ($p<0{\cdot}001$) than that of patients of group III (62%) but not than that of patients in group II (76%).

The findings suggest that the presence of CAD increases the risk of aortic valve replacement whether or not coronary artery grafting is performed. Myocardial revascularisation, however, appears to return patients with AVD and CAD to a survival curve similar to that of patients with isolated AVD

Sudden death; occurrence in 300 cases of sarcoid heart disease in the United Kingdom

H A Fleming
Papworth Hospital, Papworth Everard, Cambridge

This study investigates sudden death in the first 300 cases of sarcoid heart disease collected by the author over 15 years in the United Kingdom: 279 were white and 21 were black; 162 were male and 138 female; and the average age was 48 years. One hundred and thirty seven have died; 103 had necropsy examinations. Sudden death occurred in 77: (*a*) it was the method of presentation in 49 and (*b*) it occurred in 28 patients already diagnosed as having sarcoid heart disease. Of the 49 cases first diagnosed at necropsy, 29 were male and 20 were female, and 43 were white and 6 black. Most of the postmortem examinations were coroner's cases and they were often incomplete; however in all of them sarcoid granulomas were present in the myocardium and other organs. Massive heart involvement was frequent and the initial macroscopic label was of tumour. Occasionally the heart was unremarkable until examined microscopically. Twenty eight of the cases were from East Anglia and the rest were scattered throughout the UK, suggesting that local awareness of sarcoid heart disease was important. Twenty eight known cases of sarcoid heart disease died suddenly and 26 had postmortem examination. Nine of these examinations were considered to be substandard. Fourteen cases were known to the author in life and this interest led to the correct postmortem diagnosis finally being made. Some pathologists are reluctant to consider sudden death as being due to causes other than coronary artery disease. The commonest clinical signs of sarcoidosis were intrathoracic. In four out of 17 cases tested the Kveim test was negative. The type of cardiac presentation, treatment, and survival are considered.

Sarcoid heart disease is not rare; it is an occasional cause of sudden death and it may be overlooked even at necropsy.

The effect of aircraft vibration on the function of an activity-sensing pacemaker

W D Toff, C Leeks, M Joy, G Bennett, A J Camm
UK Civil Aviation Authority, London

The new generation of rate-responsive pacemakers includes devices incorporating a vibration sensor which influences the pacing rate relative to the perceived level of user activity. This study examined the effects on the function of such a device of extraneous vibration such as that encountered in aircraft. A bipolar Activitrax pacemaker (Medtronic, Minneapolis, USA) was attached externally to the pectoral area of a normal subject and programmed to typical settings (basic rate 60 beats/min, maximum activity rate 150 beats/min, medium activity threshold, rate response 5). The pacing rate was monitored by a Medtronic 5309 pacing system analyser incorporating a digital display and recorded every 15 seconds during flights in six fixed wing aircraft, four helicopters, and a hovercraft. In the fixed wing aircraft the maximum observed pacing rates were 115 beats/min in a light twin, 92 beats/min in a twin turboprop, and 79 beats/min in a large passenger jet. Significant increases in rate were confined to brief periods such as taxying, takeoff, turbulence, and landing, with only modest rises during most of the flights. In the helicopters and hovercraft sustained rate rises were noted throughout the flights with maxima of 100–131 beats/min. Re-setting the pacemaker activity threshold and rate response level achieved only partial reduction of the maximum rate.

Vibration associated with air travel may increase the pacing rate of activity-sensing rate-responsiveness pacemakers. In fixed wing aircraft such increases are only transient and minor but in helicopters and hovercraft they are considerable and sustained and may cause difficulty in some patients.

Comparison between maximal exercise treadmill testing and tournament squash in men over 45 years

H R Brady, T T Lynch, M R Kinirons, E M Ohman, J H Horgan
Department of Cardiology, St Laurence's Hospital, Dublin, Ireland

Treadmill stress testing is used routinely in the evaluation of cardiac symptoms experienced during competitive exercise. There are few studies comparing the physiological response to exercise in these two circumstances. We have compared the cardiovascular and metabolic responses to exercise in maximal treadmill exercise testing and competitive squash in 10 men (> 45 years). Subjects were studied at rest before exercise, on completion of exercise, and then at five and 30 minutes after exercise. The following were measured on each occasion: heart rate rhythm; potassium; catecholamines (adrenaline, noradrenaline); lactate; glucose; free fatty acids; and haematocrit. A paired Student's t test was used for statistical analysis. Treadmill exercise was associated with a higher mean (SEM) maximal heart rate (178 (3) *vs* 165 (4); $p<0\cdot05$), higher mean plasma lactate (7·4 (0·5) *vs* 5·2 (0·6 mmol/l; $p<0\cdot0025$), and higher mean plasma potassium (4·1 (0·2) *vs* 3·6 (0·14) mmol/l; $p<0\cdot05$) than squash at the end of exercise. Five minutes after squash mean serum free fatty acids were raised (0·72 (0·14) mEq/l) and mean plasma potassium was below the normal range (3·2 (0·8) mmol/l). Mean blood glucose and mean plasma catecholamines tended to be higher in squash. There was no difference in mean haematocrit between squash and treadmill exercise.

We conclude that treadmill exercise is a good reflection of the cardiovascular responses occurring during competitive squash. However, squash is associated with changes in potassium and free fatty acids which may be arrhythmogenic.

Cryoablation of the accessory pathway in Wolff-Parkinson-White syndrome: initial results and long term follow up

K Robinson, E Rowland, D M Krikler, H H Bentall
Royal Postgraduate Medical School, Hammersmith Hospital, London

Cryoablation of the accessory pathway (AP) has been used in the management of Wolff-Parkinson-White (WPW) syndrome where surgery is indicated. We examined the outcome in 17 patients who were then followed up for a mean of 5·7 (range 1–9) years. There were 10 women and seven men aged 21–58 years (mean 38·6). Indications for operation were failure of medical treatment for reentrant atrioventricular tachycardia in 11 patients and atrial fibrillation with rapid anterograde conduction across the AP in six. Thirteen patients had overt pre-excitation but it was concealed in four. The AP was located on the left free wall in nine, posteroseptally in four, on the right free wall in two, and anteroseptally in one. In one patient two APs were located on the right—one anteriorly and the other posteriorly. There was one postoperative death from rupture of an unsuspected cerebral haemangioma and one patient suffered hemiparesis. In six patients there was recurrent arrhythmia, one after one day, one after two weeks, two after one month, and two after five months. In these patients the APs were located on the left free wall in four, posteroseptally in one, and anteroseptally in the other. Reoperation was successful in four of the six; two are still managed medically, one with an anti-tachycardia device. Of the 16 survivors, 14 remain arrhythmia free.

Successful cryoablation of the AP is possible in WPW syndrome and, if arrhythmia recurs, further surgery is usually successful. Initial operative failure does not seem to be related to the site of the AP but may reflect the epicardial approach used with this technique. If surgical cure is not achieved interference with the AP may be sufficient to render the arrhythmia more amenable to medical management.

Left ventricular repolarisation sequence in man

J C Cowan, C J Griffiths, C J Hilton, J Bourke, Suda Tansuphaswadikul, A Murray, R W F Campbell
Freeman Hospital, Newcastle upon Tyne

The repolarisation sequence of intact human heart is unknown. It is widely postulated that repolarisation proceeds in the opposite direction to activation, but hitherto it has not been possible to test this hypothesis. The epicardial repolarisation sequence was studied intraoperatively in eight patients with upright T waves undergoing coronary artery bypass grafting. Monophasic action potentials were recorded from left ventricular sites (13–25 sites/patient) with a hand held probe. The left ventricle was considered as four concentric rings between base and apex. Mapping was performed during fixed rate right atrial pacing on normothermic cardiopulmonary bypass. Action potential duration increased by 30–40 ms at all epicardial sites in the first minutes of bypass. Mapping was started on return to an approximate steady state. Activation occurred earliest at the apex and latest at the base (variance analysis, $p < 0{\cdot}001$; apex − base = 18 ms (5) SEM). The action potential duration was inversely related to activation time and was longest at the apex and shortest at the base (variance analysis, $p < 0{\cdot}025$; apex − base = 16 ms (9) SEM). However, there was no significant difference in repolarisation time between the four rings (apex − base = 2 ms (5) SEM).

These findings differ from the classically postulated repolarisation sequence. They show that epicardial repolarisation is independent of activation sequence and occurs simultaneously between base and apex. The observed inverse relation between activation time and action potential duration may represent a mechanism for preserving the homogeneity of repolarisation.

Treatment with ambulatory dobutamine infusion of severe chronic heart failure refractory to current treatment

C McParland, T Gumbrielle, J Horgan
Department of Cardiology, St Laurence's Hospital, Dublin, Ireland

Severe chronic heart failure often requires repeated and prolonged admission to hospital. Thus in the absence of effective treatment to improve survival, an improvement in the quality of life is a genuine therapeutic aim. The use of dobutamine infusion in acute heart failure is well established. Therefore, we undertook an open study of continuous ambulatory dobutamine in four patients (49–60 years) with severe chronic heart failure (New York Heart Association Class III and IV) who had remained symptomatic (minimum three months), and required repeated admission to hospital despite diuretic, cardiac glycoside, and vasodilator treatment. All four had benefited from acute dobutamine and understood and participated in catheter pump care. Dobutamine (7 μg/minute) was administered via a Hickman central venous catheter by a portable infusion pump over a 48 hour period. Patients attended as outpatients for refilling of the pump at the end of each period. One patient died in hospital after eight weeks (acute pulmonary oedema) and three patients were followed up for 24–43 weeks. All four patients reported a reduction in dyspnoea, fatigue, and personal incapacity. The number of inpatient days was reduced from a mean of 64 days per patient per six month period to 0 75 days per patient per six month period. There was an improvement in clinical signs, New York Heart Association classification by at least one class, and in mean treadmill exercise duration from 3·6 to 9·75 minutes. Resting left ventricular ejection fraction assessed by radionuclide ventriculography showed no significant change. No increase in tachycardia was detected by serial Holter recording and there were no major infective or mechanical complications.

Preliminary results at six months indicate that supervised continuous ambulatory dobutamine reduces symptoms and hospital admissions, while increasing functional capacity in severe heart failure, without adverse effect on cardiac rhythm or major infection.

Left ventricular end systolic volume is the major determinant of survival after recovery from myocardial infarction

R M Norris, H D White, P W T Brandt, R M L Whitlock, C Wild
Green Lane Hospital, Auckland, New Zealand

Impairment of left ventricular function is the major predictor for mortality after acute myocardial infarction, but it is not known whether this is best described by ejection fraction or by end systolic or end diastolic volume. We measured volumes, ejection fractions, and severity of coronary arterial occlusions and stenoses in 605 male patients (< 60 years old) 1–2 months after a first (n = 443) or recurrent (n = 162) myocardial infarction, and we followed these patients for a mean of 78 months (range 15–165 months). There were 101 cardiac deaths. Multivariate analysis using log rank testing and the Cox proportional hazards model showed that end systolic volume ($\chi^2 = 82{\cdot}9$) had greater predictive value for survival than end diastolic volume ($\chi^2 = 59{\cdot}0$) or ejection fraction ($\chi^2 = 46\ 6$), while stepwise analysis showed that once the relation between survival and end systolic volume had been fitted there was no additional significant predictive information in either end diastolic volume or ejection fraction. Severity of coronary occlusions and stenoses showed additional prediction of only borderline significance (p = 0·04 in one analysis). For a subset of patients (n = 200) who had taken part in a randomised trial of coronary artery surgery after recovery from infarction, surgical "intention to treat" showed no predictive value.

We conclude that left ventricular end systolic volume is the primary predictor of survival after myocardial infarction. Treatment of infarction should be aimed at limitation of infarct size and prevention of ventricular dilatation.

Improved left ventricular function and survival after acute myocardial infarction with intravenous streptokinase: a double blind trial with and without concomitant intravenous propranolol

R M Norris, H D White, M A Brown, M Takayama, P W T Brandt
Green Lane Hospital, Auckland, New Zealand

Streptokinase 1 5 × 10^6 units or placebo was infused intravenously over 30 minutes within 4 hours (mean 3 hours) of the onset of infarction in 219 patients under 70 years of age. In 44% who did not have contraindications, intravenous propranolol followed by oral propranolol was also given, while heparin, low dose aspirin, and dipyridamole were given to all. Cineangiocardiograms were performed at three weeks after infarction in 98% of eligible patients; ejection fraction (EF) and end systolic volume (ESV) were calculated, and contractility was scored from biplane ventriculograms. Thirty day actuarial survival was improved by streptokinase (4/108 deaths among streptokinase patients *vs* 14/111 in placebo patients; p = 0·02). Survivors from first infarction who had had streptokinase showed higher EF (59 (1)% (SEM) *vs* 53 (2)%; p < 0 005), lower ESV (55 (3) ml *vs* 73 (5) ml; p < 0 005), and better contractility score (2·9 (0 3) *vs* 4·8 (0·4); p < 0·01) than those who had had placebo. Patency of the infarct related artery was 78% after streptokinase and 56% after placebo. Subgroups with anterior or inferior infarction and those who had or had not had proranolol showed similar significant benefit from streptokinase.

We conclude that intravenous streptokinase is an effective treatment and that the combination of streptokinase with intravenous propranolol is well tolerated.

Randomised trial of high dose intravenous streptokinase, of oral aspirin, and of intravenous heparin in acute myocardial infarction

R Collins, P Sleight· for the ISIS collaborative group
ISIS, Radcliffe Infirmary, Oxford

619 patients with suspected acute myocardial infarction (MI) were randomised to receive either a high dose short term intravenous infusion of streptokinase (1·5 MU over one hour) or placebo. In addition, using a "2 × 2 × 2 factorial" design, patients were also randomised to receive either oral aspirin (325 mg on alternate days for 28 days) or placebo, and separately randomised to receive either intravenous heparin (1000 IU/hour for 48 hours) or no heparin. Streptokinase (SK) was associated with a non-significant decrease in hospital mortality (7·7% in those allocated to SK *vs* 9·2% in those allocated to placebo) and an increase in non-fatal reinfarction (3·6% *vs* 2·9%). There were significantly more minor adverse events after SK (for example hypotension, allergies, bruises, or minor bleeds), but no excess of strokes or of anaphylactic shock. Aspirin was associated with fewer reinfarctions (2 9% in those allocated to aspirin *vs* 3·9% in those allocated to placebo; NS), deaths (6·1% *vs* 10·5%; 2P < 0·04) and strokes (0·3% *vs* 2·0%; 2P < 0·1). Heparin was associated with a decrease in reinfarction (1 9% in those allocated to heparin *vs* 4·9 in those allocated to no heparin; 2P < 0·04), though not in mortality (8 3% *vs* 8 2%; NS), and with a trend towards more strokes (1·6% *vs* 0·7%; NS) and more bruising and bleeding 14% *vs* 11%; NS). To assess reliably the effects of SK and aspirin on major endpoints several hundred hospitals are now collaborating in a large (about 20 000 patients planned) randomised trial (ISIS-2).

Cardiopulmonary response to dynamic exercise after combined heart-lung transplantation

N R Banner, M H Lloyd, R Hamilton, J A Innes, A Guz, M H Yacoub
Harefield Hospital, Harefield, Middlesex, and Charing Cross and Westminster Medical School, London

To determine the effect of combined heart-lung transplantation (HLT) and the resultant cardiac and pulmonary denervation on the cardiopulmonary response to dynamic exercise, we studied eight HLT recipients during symptom limited graded exercise on a cycle ergometer and compared them with eight recipients of orthotopic cardiac transplant (CT) and eight normal subjects (N) matched for age and sex. Heart rate, ECG, blood pressure, ventilation, and oxygen saturation (ear oximeter) were monitored and expired gas analysis performed with a computerised mass spectrometer. All data are quoted as mean values (SD); p values refer to comparisons with normal subjects. The maximum oxygen uptakes (l/min) of the groups were: N 1·96 (0·44); HLT 1·33 (0·45), $p<0·05$; CT 1·5 (0·62) NS. Heart rate rose with oxygen uptake in all three groups and the slopes of the regression lines (beats/litre) were: N 57·7 (15·3), HLT 28·8(14·8), $p<0·01$; CT 24·9 (13·7), $p<0·01$. Ventilation rose with oxygen uptake and the slopes of the regression lines (below the anaerobic threshold) were: N 23 9 (5·5), HLT 30·8 (6·1), $p<0\ 05$; CT 25·8 (3·2), NS. Oxygen saturation did not fall significantly during exercise. Systolic blood pressures (mm Hg) at rest were N 119 (9), HLT 108 (17), CT 108 (14) and at maximum exercise N 176 (20), HLT 146 (19), $p<0·05$; CT 148 (22), $p<0·05$. The maximum oxygen uptake of both HLT and CT recipients was lower than that of normal controls.

Both transplant groups have an abnormal heart rate response to exercise; this is related to cardiac denervation. HLT recipients also show an increased ventilatory response at submaximal workloads, which may reflect altered ventilatory control after pulmonary denervation.

Arrival-time imaging of the thoracic aorta: a new way of demonstrating the site of aortic dissection

J Lyons, A Gershlick, J Gardener, C Layton
The London Chest Hospital, London

Intravenous digital subtraction aortography (DSA) can accurately detect dissection of the thoracic aorta. Although the intimal flap can usually be distinguished from similar linear subtraction artefacts by its characteristic motion throughout the cardiac cycle, further analysis avoiding image subtraction is an obvious advantage. Since digital images are composed of a large number of pixels it is possible to compute time-density curves for each pixel throughout the period of the study. One static image depicting the time to 90% maximum density for each pixel is then constructed. Structures which do not change in density by more than 10% throughout the study, such as the background, are excluded, avoiding the need for image subtraction. Structures enhanced by contrast are depicted on a colour scale dependent on the arrival time of the contrast. Therefore, provided contrast arrives later in the false lumen, it is possible to demonstrate both the presence and, more importantly, the site of entry of the aortic dissection. This technique provides a static image of aortic dissection, which, used in conjunction with image subtraction, helps to overcome subtraction artefact. All patients with suspected aortic dissection now undergo DSA with additional arrival-time analysis.

Atrial flutter: the relation between ECG flutter waves and endocardial atrial activity and excitability

A D Cunningham, J A Kennedy, H M McAlpine, J Christie
The National Heart Hospital, London, and The Western Infirmary, Glasgow

Spontaneously occurring human atrial flutter is most commonly manifest by its surface ECG appearance of sawtooth flutter waves in the inferior leads. In 71 consecutive cases of spontaneously occurring atrial flutter, "common" flutter was present in 63 (89%). Four cases exhibited "uncommon" flutter (positive F waves in leads I and II), and in three cases no F waves were visible. Endocardial mapping was carried out in 53 cases. 220 sites were mapped (46 high anterior or lateral right atrium (HRA), 67 mid anterior or lateral (MRA), 70 low anterior or lateral (LRA), and 38 septal RA or coronary sinus). In 16 cases, 19 sites demonstrated fractionated or split electrograms (10 MRA, 9 LRA), consistent either with local block or slow activation. Split activation was more likely to occur in the mid or low anterolateral RA ($p<0·005$). Lateral RA wall activation was determined in 39 cases of common flutter (133 sites), and was upwards in seven, downwards in 27, and discordant (suggestive of local block) in five. Split potentials were present in 12 of these cases, unassociated with activation pattern. In uncommon flutter (11 sites, 4 cases), lateral RA was activated upwards in two, downwards in one, and discordantly in one. Three split electrograms were seen. When septal activation could be determined (eight cases), it was codirectional with lateral wall activation in four and opposite in four. Atrial activation was seen throughout the flutter cycle, but more RA sites (42%) were activated during the second half of the surface F wave than at any other part of the cycle. Atrial stimulation was carried out during atrial flutter at 54 sites. Fully compensatory (type II) pauses after atrial extrasystoles were seen at 17 sites and reset (type I) was observed at 37 sites. Type I response was seen most often at LRA sites (12/14), and less often at MRA (11/17), HRA (7/11), and septal (7/12) sites ($p < 0.02$). No definitive evidence for a common site of the macro reentry circuit in human atrial flutter was found. However, split or fractionated electrograms were only seen in the mid and low anterolateral RA, and were particularly associated with type I sites in the LRA. Thus it appears that the reentry circuit in human atrial flutter is more likely to involve this portion of the right atrium. This finding suggests that it may be possible to direct ablative treatment to this area.

For how long after cessation does smoking continue to act as a risk factor for the development of coronary heart disease and does the in-hospital course of a first myocardial infarction differ in non-smokers, ex-smokers, and current smokers?

K Robinson, R Conroy, R Mulcahy
Cardiac Department, St Vincents Hospital, Dublin, Ireland

We studied 978 consecutive patients admitted with a first myocardial infarction or episode of acute coronary insufficiency to examine differences between non-smokers, ex-smokers, and current smokers in risk factor profile, presentation, and in-hospital outcome. Non-smokers were older than either ex-smokers or current smokers (mean ages 65·6, 62·8, and 60·6 years respectively ($p < 0·01$). Hypertension was more common in non-smokers ($p < 0·01$) who also had a higher mean serum cholesterol concentration ($p < 0·05$). A stepwise logistic regression model selected age and hypertension as independently discriminating non-smokers from current smokers ($p < 0·01$). Applying this function to ex-smokers, patients who had stopped smoking less than 15 years before admission had a similar risk factor profile to current smokers, while those who had stopped for at least 15 years had a profile resembling non-smokers ($p < 0·05$). Non-smokers were more likely to have anterior infarctions than inferior ones ($p < 0·05$), but they had similar peak cardiac enzyme activities to ex-smokers and current smokers. Their in-hospital mortality (16·7%) was significantly higher ($p < 0·01$) than that in ex-smokers (7·2%) or current smokers (5·4%) They also had higher rates of left ventricular failure ($p < 0.01$) but not of arrhythmias or of conduction defects. When adjusted for age, site, and size of infarction and occurrence of complications, non-smokers still showed a significantly higher death rate ($p = 0·025$).

Ex-smokers may carry an increased risk of acute coronary heart disease for up to 15 years after stopping smoking. Non-smokers are older than ex-smokers or current smokers at the time of their first episode and their higher mortality may reflect more severe underlying coronary artery disease.

Plasma atrial natriuretic peptide: haemodynamic and hormonal inter-relations in cardiac impairment

A M Richards, J G F Cleland, G Tonolo, H J Dargie
Department of Cardiology and Medical Research Council Blood Pressure Unit, Western Infirmary, Glasgow

To explore the inter-relations of plasma atrial natriuretic peptide (ANP), renin, and aldosterone concentrations and haemodynamic function in cardiac impairment, we studied 63 unselected patients with cardiac lesions of a broad spectrum of type and severity undergoing diagnostic cardiac catheterisation. Plasma ANP was measured by radioimmunoassay after Sep-Pak extraction from plasma. Plasma active renin and aldosterone concentrations were also measured by radioimmunoassay. Inter-relations between plasma ANP, renin, and aldosterone concentrations were assessed both in normal subjects and in the patient group. Plasma concentrations of ANP correlated closely with New York Heart Association functional class ($r = 0.77$, $p < 0·001$), right atrial pressure ($r = 0·83$, $p < 0·001$), pulmonary arterial wedge pressure ($r = 0·65$, $p < 0·001$), and pulmonary arterial pressure ($r = 0·70$, $p < 0·001$). Among normal subjects plasma ANP concentrations were inversely related to concurrent concentrations of renin ($r = -0·52$, $n = 140$, $p < 0.001$) and aldosterone ($r = -0.38$, $n = 140$, $p < 0.001$). Plasma renin and aldosterone values correlated positively ($r = 0·55$, $n = 140$, $p < 0·001$). In contrast with the inverse relation between plasma ANP and both plasma renin and aldosterone seen in normal subjects, in the patients with cardiac impairment this relation was lost and replaced by positive associations between ANP and both renin ($r = 0.31$, $n = 60$, $p < 0·02$) and aldosterone ($r = 0.63$, $n = 57$, $p < 0.001$). However, the relation of renin to aldosterone ($r = 0·49$, $n = 58$, $p < 0·001$) was not disturbed by the very high plasma concentrations of ANP found in cardiac impairment.

ANP rises progressively with cardiac impairment. Normally plasma ANP and renin-aldosterone activity alter in a reciprocal fashion. Concurrent renin-aldosterone system activation and an increase in plasma ANP is a feature of severe cardiac disease and may reflect concurrent increases in intra-atrial pressures together with impaired renal perfusion.

Does angiotensin converting enzyme inhibition reduce myocardial ischaemia in patients with stable angina?

J S R Gibbs, P A Crean, C Wright, L Mockus, M M Shackell, G C Sutton, K M Fox
National Heart Hospital, London and Hillingdon Hospital, Uxbridge, Middlesex

Angiotensin converting enzyme inhibition reduces left ventricular diastolic pressure, aortic systolic pressure, and sympathetic drive. Such effects should reduce myocardial work and oxygen consumption and should be beneficial to patients with angina. To test this hypothesis, enalapril (10–20 mg/day) was evaluated in 12 normotensive patients (age 46–70 years mean 55) with angina and exercised induced ST segment depression. The study was randomised, double blind, placebo controlled and crossover with each treatment period lasting two weeks. Assessment was by angina diaries and maximum symptom limited treadmill exercise testing (modified Bruce protocol). All medication except glyceryl trinitrate was stopped seven days before the start of the study. The results for the group as a whole showed a reduction in mean (SD) systolic blood pressure at rest from 134(16) to 118(15) mm Hg ($p<0{\cdot}05$) and at peak exercise from 165(30) to 146(27) mm Hg ($p<0{\cdot}05$). Heart rate at rest and at peak exercise was unchanged. Frequency of angina attacks and consumption of glyceryl trinitrate were unaltered by enalapril. Total exercise duration on enalapril increased from 466(94) to 509(115) seconds (NS) and exercise duration to 1 mm ST depression from 345(77) to 387(114) seconds (NS). By contrast with these findings for the group, four patients had striking prolongation of total exercise time (mean 450 to 591 seconds) and exercise duration to 1 mm ST depression (mean 315 to 435 seconds).

Although enalapril was not effective in reducing myocardial ischaemia in the group as a whole, some patients were substantially improved.

Provocation of ventricular tachycardia by high energy catheter ablation of normal atrioventricular conduction

D W Davies, A W Nathan, J L Caplin, A J Camm
St Bartholomew's Hospital, London

Catheter ablation of normal atrioventricular (AV) conduction is now the treatment of choice for many refractory supraventricular arrhythmias. Although it is successful in about 90% of patients a few have subsequent ventricular tachycardia (VT) and sudden death. Because these might have been caused by the ablation procedure we prospectively searched for VT in 11 of our patients undergoing catheter ablation of normal AV conduction for refractory supraventricular arrhythmias. All patients had ambulatory ECG recording before and after ablation and were studied during programmed ventricular stimulation by a standard stimulation protocol immediately before and 2–4 days after the procedure.

No patient died during a follow up (15 to 26 months (mean 20·5)). None of the ambulatory ECGs showed VT before or after ablation. In eight patients VT was not inducible at either stimulation study. Non-sustained VT was inducible in one patient with equal facility before and after the ablation. VT occurred spontaneously in two patients within 24 hours of the ablation. Emergency cardioversion was required in one but VT was not inducible at the stimulation study performed three days after ablation and has not recurred. In the other patient with early spontaneous VT, the same VT was reproducibly initiated at subsequent stimulation studies and this patient required prophylactic treatment 25 months afterwards. One patient had asymptomatic non-sustained VT (4 beats) documented once during follow up eight months after ablation.

VT may be unpredictably provoked by high energy catheter ablation of normal AV conduction and usually presents soon after ablation; it should be sought and may require longer term treatment.

A longitudinal study of smooth muscle cell turnover within and platelet deposition on experimental vein grafts

J C Chalmers, Denise Syndercombe Court, R Bush, C T Lewis, P G Mills
The London Hospital, London

Intimal thickening is an important cause of the long term failure of vein grafts. We used a rabbit model to assess the time course of platelet deposition and smooth muscle cell turnover in grafted vessels. In separate operations, one or two weeks apart, according to group, each animal received two jugular vein grafts into the carotid artery. Groups of rabbits were killed three and five weeks and three and six months later and the grafts were harvested. Twenty four hours before death autologous platelets labelled with indium-III tropolonate were injected and 45 minutes before death each rabbit received a pulse dose of tritiated [3H] thymidine. Measurement of platelet deposition on one graft was derived from indium-III counts of the vessel and a blood standard. Platelets × 10^6 g graft tissue (mean (range)) in each group were: three weeks 244 (87–472), n = 5; five weeks 189 (111–317), n = 7; three months 101 (52–218), n = 6; six months 111 (65–154), n = 6. One three week old graft and one six month old graft were blocked; two grafts were contaminated with postmortem clot and these were not measured. Intima was stripped mechanically from the other graft and the [3H] thymidine uptake per µg DNA was compared with the mean measure obtained from the abdominal and thoracic aortas of the same animal. The ratio graft: aorta (mean (range)) in each group was: three weeks 16·9 (5·2–27·6), n = 6; five weeks 11·6 (6·2–17·0), n = 4; three months 2·2 (0·6–4·8), n = 7; six months 2·0 (0·9–3·6), n = 6. In three grafts, one each from the five week, three week, and six month groups, no intima or turnover could be detected. The activity of smooth muscle cell turnover rose and fell in parallel with platelet deposition. At six months while platelet deposition appears to have reached a steady state, the rate of smooth muscle cell turnover in the grafted tissue was still double that observed in the aorta. Any treatment that might be directed against smooth muscle cell turnover in order to reduce graft intimal thickening therefore needs to continue for at least six months after grafting.

Morphology of coronary arterial lesions and early thrombotic occlusion after percutaneous transluminal coronary angioplasty

M Been, M Buchalter, D S Reid, D O Williams, O Weldon
Regional Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne

Early thrombotic occlusion occurred in eight (24%) of 33 consecutive patients who intitially had successful percutaneous coronary angioplasty (PTCA) for unstable angina. Five of these had successful repeat PTCA and three had emergency coronary bypass grafting. This unexpectedly high event rate led us to analyse the coronary artery lesion morphology to determine whether it was possible to predict those at risk from early thrombotic occlusion. The coronary artery lesions were retrospectively analysed by two angiographers who did not know the outcome of the PTCA. The coronary lesions were classified into three groups according to their complexity and irrespective of the severity of the stenosis. Eight patients had symmetrical smooth lesions (type 1), nine patients had asymmetrical smooth lesions (type 2), and sixteen patients had more complex asymmetrical, irregular, or "punched out" lesions (type 3). Clinical characteristics were similar in the three groups. One of the eight patients with type 1, one of the nine with type 2, and six of the 16 with type 3 lesions had early thrombotic occlusion.

Although PTCA is an effective treatment for unstable angina patients with unstable angina and angiographic complex lesions are at risk from early thrombotic occlusions after PTCA.

Possible pitfalls when mean aortic valve gradient alone is used to grade aortic stenosis

M J Griffith, C M Carey, D J Coltart, B S Jenkins, M M Webb-Peploe
Cardiac Department, St Thomas's Hospital, London

Echocardiographic and Doppler estimation of mean aortic valve gradient (MAVG) compares well with invasive measurements. Although MAVG gives an approximate assessment of the severity of aortic stenosis misclassification may occur with abnormal stroke volumes. This is a particular problem when echocardiographic and Doppler determination of stroke volume is unreliable, for example in mixed aortic valve disease or left ventricular dilatation. Gorlin's formula for aortic valve area (GAVA) incorporates stroke volume and is accepted as a good measure of the severity of aortic stenosis. Therefore, we compared MAVG with GAVA to see how frequently MAVG alone would misclassify aortic stenosis. 636 patients with aortic stenosis (with or without regurgitation) who had undergone full cardiac catheterisation were reviewed. Patients with mitral valve disease were excluded. MAVG and systolic ejection period were averaged over at least five beats. Cardiac output was determined by dye dilution unless there was significant aortic regurgitation, in which case angiographic data on ventricular volume were used. GAVA was calculated and then compared with MAVG. We looked for a value of MAVG which could be used as a sensitive and specific predictor of critical aortic stenosis (GAVA < 0·75 cm^2). With MAVG > 30 mm Hg there were few false negatives (16/165 (9%)) but many false positives (139/471 (29%)), giving a sensitivity of 95% and a specificity of 48%. MAVG > 60 mm Hg gave far fewer false positives (26/210 (12%)) but more false negatives (164/426 (38·5%)) with a sensitivity of 53% and specificity of 91%. All patients with MAVG $>$ 110 mm Hg had critical aortic stenosis and no patient with MAVG $<$ 20 mm Hg had critical aortic stenosis. However, these limits included only 11% of patients. These results demonstrate the importance of measuring stroke volume in all patients when echocardiographic and Doppler are used to evaluate aortic stenosis.

Infarct sizing: comparison of technetium-99m pyrophosphate tomography and creatine kinase-MB release

P S Robinson, C M Tonge, M D Joy
St Peter's Hospital, Chertsey, Surrey

Measurement of the extent of myocardial necrosis provides a major predictor of morbidity and mortality after infarction and is important for the assessment of interventions to limit infarct size. Release of myocardial creatine kinase (CK-MB) is used as a reference technique but release kinetics may be affected by interventions such as thrombolysis. Imaging acute infarction with technetium-99m pyrophosphate offers qualitative information but the determination of infarct volume by single photon emission tomography (SPECT) should provide quantitation of the extent of necrosis. We have studied 20 patients admitted to a coronary care unit within six hours of the onset of acute infarction. The extent of myocardial necrosis was determined by measurement of CK-MB release over 96 hours after the onset of symptoms. Planar and SPECT pyrophosphate myocardial imaging was undertaken between 24 and 72 hours after infarction. In 17 patients with uncomplicated acute infarction a good correlation was demonstrated between cumulative CK-MB release and the volume of myocardial pyrophosphate uptake measured by SPECT ($r = 0{\cdot}92$). Similar correlations were obtained for eight patients with anterior infarction ($r = 0{\cdot}90$) and nine patients with inferior infarction ($r = 0{\cdot}94$). SPECT provides a more accurate measurement of the extent of myocardial necrosis than that obtained from planar imaging and offers advantages in terms of infarct localisation. Three patients were given intravenous streptokinase within four hours of the onset of major symptoms and substantial alterations of CK-MB release kinetics were demonstrated. In this limited study the relation between cumulative CK-MB release and myocardial pyrophosphate uptake appeared to be maintained.

Technetium-99m pyrophosphate myocardial SPECT is a promising technique for sizing acute infarction. The technique is not influenced by the site of infarction and may have advantages when interventions that alter myocardial enzyme release kinetics are used. Further studies in the setting of intervention with tissue plasminogen activator are planned.

Significance of left ventricular gradient in hypertrophic cardiomyopathy

Y Yonezawa, Shaughan Dickie, P Nihoyannopoulos, J P Lavender, Celia M Oakley, W J McKenna
Royal Postgraduate Medical School, Hammersmith Hospital, London

The significance of left ventricular (LV) gradients in hypertrophic cardiomyopathy (HCM) is controversial. To assess the proportion of stroke volume left in the left ventricle at the onset of systolic anterior motion (SAM) of the mitral valve we performed concurrent technetium-99m radionuclide cineangiography and colour flow mapping with continuous and pulsed wave Doppler echocardiography in 41 consecutive patients with HCM. Twelve had complete SAM with septal contact, 14 had incomplete SAM without septal contact, and 15 did not have SAM; none had moderate/severe mitral regurgitation. The peak velocity of blood flow was significantly greater in complete SAM (3·8 (1) m/s *vs* incomplete 1·8 (0·3) and *vs* no SAM 1·4 (0·3) m/s). Radionuclide peak ejection rates (3·9 (0·7), 3·9 (0·8) and 3·9 (1·0) EDV per s and ejection fraction (78 (9), 76 (8), and 75 (7) per cent) were similar. The time from the R wave to the onset of SAM septal contact was 232 (37) ms. The proportion of stroke volume ejected by SAM septal contact in patients with complete SAM was 48-89%, median 72 (14), and after 230 ms in patients with incomplete SAM and no SAM it was 70 (10) and 73 (14) per cent respectively. In patients with complete SAM the magnitude of the LV gradient was inversely related to the proportion of stroke volume ejected ($r = 0{\cdot}71$, $p < 0{\cdot}01$).

These findings suggest that HCM with or without a LV gradient is associated with rapid, early, and near complete systolic emptying, but in a minority, particularly those with early onset of SAM and large gradients, there is considerable residual stroke volume after SAM septal contact that is consistent with "obstruction".

Serodiagnosis of *Streptococcus faecalis* endocarditis by immunoblotting of surface protein antigens

Grace Smith, I D Farrell, Eileen Aitchison, P A Lambert
Public Health Laboratory, East Birmingham Hospital, and Department of Pharmaceutical Sciences, Aston University, Birmingham

Endocarditis caused by *Streptococcus faecalis* is becoming more common, particularly in elderly men, and the condition remains difficult to treat. Surface protein antigens, expressed by serum-grown bacterial cells, have been used as the basis for a serodiagnostic test for *S faecalis* endocarditis. Three major species specific surface protein antigens, molecular weights 73, 40, 37 kd, can be demonstrated after separation of bacterial components by sodium dodecyl sulphate polyacrylamide gel electrophoresis followed by electrophoretic transfer on to a nitrocellulose membrane. The antigens are incubated with serum from patients with endocarditis and the antibodies that react with antigens on the membrane are visualised with a protein A-horseradish peroxidase conjugate. Antibody to at least one of the species specific antigens was detected in the serum of all six patients with *S faecalis* endocarditis who were tested. Serum antibodies to antigens prepared from other species of streptococci were not detected in any of these patients. Serum from 129 patients with various infections did not react with any of three species specific antigens. These included serum from patients with endocarditis caused by microorganisms (32), a septicaemias (34), *S faecalis* infections at other sites (50), and patients undergoing continuous ambulatory peritoneal dialysis (13). False positive reactions were seen in serum from three patients, however; one patient had had an episode of *S faecalis* endocarditis six months before collection of serum for the test; one had prolonged *S faecalis* colonisation of a nephrostomy tube, and one had endocarditis caused by a nutritionally variant streptococcus.

Prognostic criteria in post-infarction ventricular septal defect

G D Angelini, W J Penny, M S T Ruttley, A H Henderson
Cardiac Unit, University Hospital of Wales, Cardiff

Mortality from post-infarct ventricular septal defect can be reduced by operation, selection for which would be helped by knowledge of factors affecting postoperative prognosis. We reviewed our eight year experience of 38 surgically treated patients, and compared the preoperative characteristics in those who died postoperatively (14) with those who survived (24, all still alive). Sex, age, infarct size (peak creatine kinase), left ventricular end diastolic pressure, pulmonary:systemic flow ratio (3·1 (0·8) *vs* 3·0 (0·7), mean (SE)), and blood urea were similar in the two groups. Non-survivors had significantly more inferior myocardial infarction (57 *vs* 21%), cardiogenic shock (64 *vs* 29%), right ventricular coronary perfusion graded (on the basis of assessment, blind of outcome, of angiographic anatomy, site of occlusion or stenosis, and overt collateral supply) as bad (8/11 *vs* 1/19), and higher right ventricular end diastolic pressure (15·0 (1·0) *vs* 11·2 (1·1) mm Hg). Of the nine with inferior infarcts who had angiography, four graded as having bad right ventricular perfusion all died; only one of the other five died (from incidental haemorrhage). Of the 21 patients with anterior infarcts by angiography, four of the five graded as having poor right ventricular perfusion died; only two of those graded as having good right ventricular perfusion died (one from perioperative inferior infarct and one with grossly impaired left ventricular function).

Prospective evaluation of factors predictive of outcome singly or in combination may help to identify those patients most likely to benefit from operation. The data show the importance of right ventricular function. The angiographic findings raise the possibility that prognosis might be improved by revascularisation or mechanical support or both where right ventricular perfusion is compromised.

Recombinant tissue plasminogen activator in the early phase of acute myocardial infarction

A J McNeill, J S Shannon, S R Cunningham, D J Flannery, N P S Campbell, M M Khan, G C Patterson, S W Webb, A A J Adgey
Regional Medical Cardiology Centre, Royal Victoria Hospital, Belfast, Northern Ireland

Thirty six consecutive patients (30 men, 6 women; mean age 58 years (42–71)) were randomised at 20–240 minutes (mean 140) from onset of pain to receive 20, 50, or 100 mg of recombinant tissue plasminogen activator (rt–PA) by intravenous infusion over 90 minutes. At 90 minutes coronary angiography was performed. Fifteen patiens had grade 3, 6 had grade 2, nine had grade 1, and six had grade 0 reperfusion of the infarct related artery (0 vessel occluded, 3 distal flow as rapid as in a non-infarct related artery). Grade 2 or 3 reperfusion occurred in four of the 12 on 20 mg, seven of the 12 on 50 mg, and ten of the 12 on 100 mg. All nine patients given rt–PA up to 80 minutes after the onset of pain had ≥ grade 2 reperfusion. Thirty four of the 36 patients received a further 50 mg rt–PA iv over 1–5 hours. Heparin was then started in 33 patients and continued for 1–10 days. During hospital admission three patients developed clinical signs of reocclusion proven in two at repeat angiography. Gated blood pool scans in 27 patients at an average of 43 hours (16–104) after the onset of pain and regional third ejection fractions (RTEFs) calculated for septal, inferior, and posterior segments from the left anterior oblique 45° views showed that the infarct related RTEF for 13 patients with grade 2 or 3 reperfusion was 50·3 (4·98%) (mean (SEM)) whereas for patients with grade 0 or 1 reperfusion it was 32·3 (5·1%). Peak creatine kinase MB ranged from 31 to 1009 and peak total creatine kinase from 302–24 060 U/l (normal CK–MB up to 25 and CK 140 U/l). During rt–PA there was a slight reduction in serum fibrinogen. No significant bleeding occurred during rt–PA, and during heparin one patient required one unit of blood. During hospital admission, four patients died from cardiogenic shock.

rt–PA (100 mg) is a most effective thrombolytic agent. When it was administered within 80 minutes of onset of chest pain rt–PA allowed reperfusion regardless of dose. Reocclusion, bleeding complications, and reduction in serum fibrinogen were minimal.

Haemodynamic response to ibopamine: evidence for differential activity on the venous and arterial sides

K J Hogg, R S Hornung, C A Howie, W S Hillis
Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow

Ibopamine is an orally active dopamine derivative which has been used as a positive inotrope in patients with congestive cardiac failure (CCF). The haemodynamic effects of an oral dose of 200 mg ibopamine were measured invasively in eight patients who had significant left ventricular dysfunction (pulmonary capillary wedge pressure ≥15 mm Hg). A thermodilution balloon catheter was placed in the pulmonary artery to record right atrial pressure (RAP), pulmonary arterial pressure (PAP), wedge pressure (PCWP), and cardiac output (CO). The aortic and left ventricular pressures were measured and the contractility indices dP/dt and dP/dt p′ derived. Baseline values were recorded and measurements were made every 15 minutes for an hour after dosing. A rise in cardiac output from 5·9 (1·6) l/min to 7·5 (1·1) l/min ($p<0{\cdot}05$) was seen at 45 minutes with a concomitant rise in heart rate from 73 (9) beats/minute to 93 (24) beats/minute ($p<0{\cdot}01$). The systemic vascular resistance showed an early fall from 1435 (357) pre-dose to 1227 (351) dyne $\mathrm{s}^{-1}\,\mathrm{cm}^{-5}$ at 15 minutes which was sustained at one hour. However, an early rise in right sided venous pressures was seen at 15 minutes, the RAP rising from 4 (2) mm Hg to 7 (2) mm Hg ($p<0{\cdot}05$) and returning to baseline values at one hour. Similar profiles were seen with mean PAP (23 (8) mm Hg to 34 (10) mm Hg at 15 minutes ($p<0{\cdot}001$) and mean PCWP (14·6 (7) mm Hg to 25 (13) mm Hg at 15 minutes ($p<0{\cdot}01$)). There was a smaller rise in left ventricular end diastolic pressure at 15 minutes from 27 (5·5) mm Hg to 33 (6·0) mm Hg. The derived indices of contractility, dP/dt and dP/dt p′, showed a moderate rise at 45 minutes (1356 (254) pre-dose to 1854 (589) and 22·1 (4·8) pre-dose to 24·6 (3·4) respectively (NS)). These results suggest a differential effect on venous and arterial sides which may be explained by selective pulmonary venoconstriction or differential stimulation of α and β receptors.

The need for coronary arteriography in patients with aortic valve disease

C M Carey, M J Griffith, D J Coltart, B S Jenkins, M M Webb-Peploe
Cardiac Department, St Thomas's Hospital, London

It has been suggested that because of improvements in non-invasive assessment of patients with aortic valve disease (AVD) preoperative cardiac catheterisation may be unnecessary, particularly if there is no history of chest pain. It is known that some patients with AVD have significant coronary artery disease (CAD) despite the absence of chest pain. How large is this group and does it have any distinguishing features? Over a 12 year period 921 adults underwent cardiac catheterisation to assess the severity of AVD. Right and left heart catheterisation and coronary arteriography were performed in all cases. Patients with mitral valve disease were excluded. 481 patients had angina or atypical chest pain and 170 (35·3%) of these had CAD. 440 patients gave no history of chest pain; 73 (16·6%) of these patients had CAD. Comparison of the subgroup without chest pain with the overall group showed that patients without pain were older ($p<0{\cdot}00001$) and had a higher incidence of syncope ($p<0{\cdot}0007$). Differences in other risk factors including sex, family history of CAD, other vascular disease, smoking, diabetes, and hyperlipidaemia, however, were not significant. In the group without pain the youngest man was aged 40 and the youngest woman 56. In the total group there were 242 patients aged <50 of whom 12 men and two women had CAD. No patient aged <40 (n = 100) had CAD although two had important coronary artery anomalies. In the group of patients without chest pain aged >40 (n = 378) 19·3% had CAD.

These findings suggest that even when there is no history of chest pain there is an appreciable frequency of CAD in patients with AVD aged >40. At present coronary arteriography is the best method of identifying this group.

Myocardial capillary basement membrane thickness in young diabetics

C Sutherland, B M Fisher, B M Frier, G B Lindop, H J Dargie
Western Infirmary, Glasgow

Previously we have reported an impaired ejection fraction response to exercise in young diabetics. To investigate the contribution of small vessel disease to this abnormality of ventricular function, we compared endomyocardial right ventricular biopsy specimens from seven symptom free type 1 (insulin dependent) diabetic patients aged 30–50 years with biopsy specimens from seven non-diabetic age and sex matched controls examined by light and electron microscopy. The diabetic patients had normal coronary arteriograms but all showed a reduced ejection fraction on exercise. Myocardial capillary basal laminar thickness was measured by electron microscopy. No significant difference in basal laminar thickness was demonstrated between diabetic (mean 79·3 nm) and control patients (mean 73·0 nm). Light microscopy showed significant but non-specific interstitial fibrosis in five diabetic patients and arteriolar thickening in two diabetic patients.

Thus impaired ventricular function in young asymptomatic type 1 diabetics is associated with significant histological abnormalities. These, however, are not related to coronary artery disease or to capillary basement membrane thickening which has been described as a characteristic feature of diabetic capillaries in several other organs including kidney, skin, and skeletal muscle.

Rapid termination of supraventricular tachycardia in children by adenosine

B Clarke, Janice Till, E Rowland, D E Ward, P J Barnes, E A Shinebourne
Brompton Hospital, London

The purine nucleoside adenosine is an effective antiarrhythmic agent in man, impairing atrioventricular nodal conduction and thereby terminating reentrant supraventricular tachycardia (SVT). Three neonates and one older child (aged 10 years) presented with seven episodes of SVT refractory to other agents. The neonates were all in cardiac failure because of prolonged SVT associated with the presence of an accessory pathway. The older child underwent electrophysiological study for investigation of recurrent atrioventricular nodal tachycardia. In each case adenosine was given intravenously in increments of 0·05 mg/kg, up to a maximum of 0·25 mg/kg. Termination of tachycardia was achieved in each case within 20 seconds of injection (range 9–20). No change in blood pressure was observed in any instance. In two patients inspection of the ECG immediately after termination of the tachycardia allowed a definitive diagnosis of the mechanism. The presence of atrial echo beats in one child and anterograde conduction down an accessory pathway in another (the appearance of delta wave on the ECG) provided evidence of a potential reentry circuit.

Adenosine is a safe and effective drug for the diagnosis and short term termination of SVT in severely ill children. The very short half life in human blood (10–20 seconds) allows rapid and accurate dosage titration and ensures that any possible side effects are transient.

Haemodynamic changes during early human pregnancy: an M mode and Doppler echocardiographic study

S C Robson, R Boyes, W Dunlop, S Hunter
Freeman Hospital, Newcastle upon Tyne

Many of the haemodynamic changes that occur during pregnancy are thought to occur during the first trimester but the size and timing of these changes have not been adequately documented. We have used cross sectional, M mode, and Doppler echocardiography to study the changes in cardiac haemodynamic function during the first trimester of pregnancy. Twelve women were recruited before conception Investigations were performed on day 21 of two consecutive menstrual cycles. After conception, investigations were repeated 5, 8, and 12 weeks after the last menstrual period. Mean (SEM) cardiac output has increased from 4·85 (0·11) l/min to 5·42 (0·11) l/min by five weeks ($p<0·001$). This increase was primarily due to an increase in heart rate from 74 (1) to 79 (1) beats/min ($p<0·01$). By 12 weeks cardiac output had increased to 6·58 (0·11) l/min ($p<0·001$) due to a further increase in heart rate to 83 (1) beats/min ($p<0\cdot001$) and an increase in stroke volume from 65·1 (1·0) to 79·9 (1·9) ml ($p<0\cdot001$). End diastolic left ventricular dimension and left atrial dimension had increased by eight weeks ($p<0\cdot001$). Myocardial contractility, as measured by M mode echocardiography, had increased by five weeks ($p<0\cdot001$).

Cardiovascular adaptation occurs earlier in pregnancy than previously reported. Echocardiography is ideally suited to the measurement of haemodynamic changes during pregnancy.

Atrioventricular relations during tachycardia: are they useful for diagnosis?

D W Davies, C Sponzilli, Elizabeth B Cornu, Lorraine K Holley, D A Richards, A J Camm
St Bartholomew's Hospital, London and Westmead Hospital, Sydney, Australia

Analysis of the temporal relation of atrial and ventricular depolarisation may allow recognition of tachycardia by implanted dual chamber devices especially if atrioventricular or ventriculoatrial block is present. Difficulty arises when there is a 1:1 atrioventricular relation in tachycardia. We therefore examined the temporal relations of atrial (A) and ventricular (V) electrograms obtained at clinical electrophysiology studies during sinus rhythm and 58 episodes of junctional reentry tachycardia (JRT) from 58 patients aged from 6 to 72 (mean 38·2) years; 26 had ventricular preexcitation. There were 28 episodes of atrioventricular nodal reentry tachycardias, 30 of atrioventricular reentry tachycardias with 18 left (four concealed), 10 septal, and two right sided accessory pathways. If sinus rhythm was not preexcited, the AV interval was corrected to JRT rate by Lepeshkin's formula (SRc) but the AV interval was assumed to remain constant at all rates with preexcited sinus rhythm. The ratio of AV:VA intervals present during JRT was then compared with those during sinus rhythm of JRT rate.

AV:VA ratios (mean and range) for SRc *vs* JRT were respectively: 0·51 (0·33–0·81) *vs* 16·5 (2·7–70) for atrioventricular nodal reentry tachycardias; 1·47 (0·24–4·25) *vs* 1·94 (0·5–4·25) for atrioventricular reentry tachycardias with septal accessory pathways; 1·16 (0·7–1·61) *vs* 1·78 (0·96–3·15) for atrioventricular reentry tachycardias with overt left accessory pathways; 0·77 (0·64–0·91) *vs* 1·69 (1·17–2·13) for atrioventricular reentry tachycardias with concealed left accessory pathways; and 0·77 (0·29 and 0·48) *vs* 1·62 (1·14 and 2·09) for atrioventricular reentry tachycardias with right accessory pathways. AV:VA ratio analysis reliably allowed distinction between atrioventricular nodal reentry tachycardia and sinus rhythm with wide differences always present. Individual and overall similarities of AV:VA ratios in preexcited sinus rhythm and atrioventricular reentry tachycardias make distinction of these unreliable by this method.

Rate responsive pacing: is there already a dual sensor system?

S C Webb, L M Lewis, Jayne A Morris-Thurgood, R G B Palmer, J E Sanderson
Royal Postgraduate Medical School, London and Musgrove Park Hospital, Taunton, Somerset

Respiratory dependent pacemakers sense regional variations in chest wall impedance and increase the heart rate in response to exercise induced hyperventilation. We have observed disproportionate increases in heart rate during certain forms of exercise, suggesting that the sensor also responds to non-respiratory movement. To test this hypothesis, ECG telemetry was used to record the heart rate response to a range of activities in five patients with complete heart block and respiratory dependent pacemakers (Biotec RDP3). Heart rate rose from 72(2) beats/min, mean (SEM)) at rest to 115(6) when patients were walking normally but fell to 88(6) during continued walking with restricted arm movement. Voluntary hyperventilation while standing still caused heart rate to rise to a peak of 96(7) beats/min. Heart rate increased to 119(11) beats/min when the arm ipsilateral to the pacemaker was swinging regularly but only reached 88(4) when the contralateral arm was swung.

The sensitivity of the respiratory sensor to arm movement should be taken into account when programming the RDP3 pacemaker and may profoundly affect the heart rate response to different forms of daily exercise. Appropriate signal processing may enable a single sensor to respond to both respiration and activity. These could then provide the inputs for a dual sensor rate responsive algorithm.

A transseptal aortic balloon valvotomy

J C P Crick, G J Davies, M Impallomeni, Celia M Oakley
Hammersmith Hospital, Royal Postgraduate Medical School, London

Aortic valvotomy by balloon catheter offers the hope of at least temporary relief of severe stenosis in patients unable to undergo valve replacement. Two major technical problems have been encountered when performing aortic valvotomy by the retrograde approach. The balloon position becomes unstable during inflation and removal of the deflated balloon through the arteriotomy causes local damage and consequent difficulty with haemostasis. An alternative technique has been devised that uses the femoral venous route to pass a guide wire across the atrial septum to the left ventricle and through the aortic valve. The dilatation catheter, single balloon type, is then passed over the wire and across the aortic valve. Traction applied to the catheter easily prevents systolic propulsion of the balloon into the aorta during inflations to 4 bar. Initial clinical experience showed that this technique overcame both problems and was successful in reducing the transvalvar gradient by >50% with no aortic regurgitation. There were no difficulties in crossing the septum with the balloon catheter and no subsequent shunt at atrial level.

We conclude that the transeptal venous route may be preferable for aortic valvotomy. Further favourable experience may widen the indications for the procedure and justify a randomised trial to compare its results with those of surgery in elderly patients.

A comparison of the effects of substance P and calcitonin gene related peptide on resistance vessels and veins in man

J R McEwan, N Benjamin, S Larkin, R W Fuller, I MacIntyre, C T Dollery
Departments of Clinical Pharmacology, Medicine, and Chemical Pathology, Royal Postgraduate Medical School and Department of Pharmacology, St George's Hospital Medical School, London

The localisation of neuropeptides in the cardiovascular system has suggested a physiological role for peptidergic nerves in cardiovascular regulation. We compared the effects of substance P and calcitonin gene related peptide (CGRP) on resistance vessels, by measuring forearm blood flow by venous occlusion plethysmography during brachial artery peptide infusion, and also on the tone of superficial veins at rest after preconstriction by noradrenaline or after constriction stimulated by the single deep breath reflex. Incremental doses of CGRP caused a dose dependent increase in forearm blood flow (from 3·28 (0·56) to 9·08 (2 12) ml/min/100 ml forearm volume at 10 pmol/min ($n = 6$, $p < 0{\cdot}01$, analysis of variance). Substance P caused a dose dependent increase in forearm blood flow from 2·18 (0·39) to 6·14 (1·72) ml/min/100 ml at 1·5 pmol/min. During a 30 min infusion of substance P the initially increased flow decreased, suggesting tachyphylaxis; increased flow caused by CGRP was maintained. The biological effective half life of CGRP was 18 minutes while that of substance P was approximately 15 seconds. Venous infusion of substance P did not affect resting venous tone but it relaxed those veins constricted by noradrenaline and also inhibited the venoconstrictor reflex. The lowest-effective dose of substance P was 100 fmol/min but there was rapid development of tachyphylaxis and a dose response curve could not be constructed. CGRP had no effect on the veins.

CGRP and substance P have different patterns of onset and offset of actions and tachyphylaxis, suggesting different modes of action on blood vessels, though both may be involved in the control of vascular smooth muscle tone.

Good Hearted Glasgow: The Greater Glasgow Health Board multiple risk factor intervention programme for cardiovascular disease

Elaine McCabe, Patricia M Birkett, L A G Davidson
Department of Community Medicine, Greater Glasgow Health Board, Glasgow

Scotland now has the highest standardised mortality rate (SMR) for coronary heart disease (CHD) in the world. The Glasgow SMR is 10% higher than that in the rest of Scotland. 45% of all deaths in Glasgow are caused by CHD and stroke. The daily average bed use in Glasgow for the management of all aspects of CHD and stroke is 1294 of which 418 are in the acute sector. The estimated hospital inpatient cost to the Health Board is over £30 million per annum excluding medical costs. The Glasgow MONICA Project has confirmed that over 75% of sudden deaths due to CHD occur before the victim can be admitted to hospital. In May 1985 the health board committed itself to a 10 year multiple risk factor intervention programme at an estimated overall cost of £8 million with the object of reducing the incidence and effects of CHD in Glasgow by 10% in 10 years. The strategy adopted is to provide a major community education programme about alterable risk factors and improved life style:

(a) By further developing the Glasgow 2000 Campaign to make Glasgow a smoking free city by the year 2000.
(b) By issuing dietary guidelines based on the Committee on the Medical Aspects of Food Policy Report, including animal fat reduction by 25% with substitution of unrefined carbo-

hydrate and fibre and promotion of increased physical activity.

(c) By providing, through general practice, screening of all Glaswegians aged between 20 and 50 (an estimated population of 400 600) for assessment of general health state, blood pressure, and blood cholesterol. Subjects with abnormal findings will be absorbed into the primary care and hospital system as appropriate. Following guidelines laid down in the Manual of Recommended Practice, individualised advice will be available to all persons screened.

(d) By developing community networks and special intervention for special groups.

The project and a pilot campaign covering 20% of the Glasgow population will be reported. Full coverage will be available by 1988.

Effects of lower body positive pressure on plasma atrial natriuretic peptide and sodium excretion in cardiac transplant patients

M D Gammage, M R Wilkins, L B Tan, H M Lewis, W A Littler
Departments of Cardiovascular Medicine and Clinical Pharmacology, East Birmingham Hospital, Birmingham

Animal studies have suggested that the renal response to increased atrial pressure (a stimulus to atrial natriuretic peptide (ANP) release) is impaired after cardiac denervation. Recipients of cardiac transplants provide a model of cardiac denervation in man. Lower body positive pressure (LBPP) increases atrial dimension and circulating immunoreactive ANP (Ir-ANP) activity in healthy volunteers. We have studied the effect of LBPP on Ir-ANP, water, and sodium excretion in five cardiac transplant recipients (mean (SE) age 48 (4) years; mean (SE) time post-transplant 33 (10) months) and compared the data with those from 10 healthy volunteers (mean age 25 (1) years). All subjects followed the same protocol on each of two days; on one day LBPP was applied by inflation of a Medical Anti-Shock Trouser (MAST) suit to 40 mm Hg for one hour. Basal Ir-ANP was 58·7 (12·6) pmol/l in transplant patients and 7·0 (1·0) pmol/l in volunteers ($p < 0.01$). After 20 minutes of LBPP, Ir-ANP was unchanged in transplant patients but had risen to 11·1 (1·4) pmol/l in volunteers ($p > 0.05$ compared with basal). After 60 minutes of LBPP, Ir-ANP was increased in transplant patients (94·0 (15 1) pmol/l; $p < 0.05$) and remained increased in volunteers (11·6 (0·9) pmol/l). Thirty minutes after removal of LBPP, Ir-ANP had returned to basal values in both groups. Sodium excretion and urine flow in transplant patients were unaffected by LBPP but sodium excretion increased after LBPP (85 3 (9·2) to 117·2 (14·1) µmol/min; $p > 0.05$) and urine flow increased during LBPP (2·6 (0·5) to 6·7 (0 8) ml/min; $p < 0.05$) in volunteers.

These data confirm the increase in basal ANP in cardiac transplant recipients and suggest a blunting of the ANP response to LBPP. Furthermore, cardiac denervation in man appears to attenuate the natriuretic and diuretic response to LBPP.

Is ventricular fibrillation complicating acute myocardial infarction a reperfusion arrhythmia?

J C Cowan, M Been, I Gibb
Freeman Hospital, Newcastle upon Tyne

Spontaneous reperfusion in acute myocardial infarction (AMI) is relatively common. For this reason it has been suggested that ventricular fibrillation (VF) complicating AMI may be a reperfusion arrhythmia. This suggestion was investigated by comparing profiles of creatine kinase (CK) release in VF patients with profiles in patients in whom the reperfusional state was determined angiographically. Nine patients with AMI who developed primary VF within four hours of the onset of symptoms were studied. Blood samples were drawn four hourly for CK estimation. The enzyme curves were compared with curves from 27 patients with AMI who received intravenous thrombolytic treatment within four hours of the onset of symptoms and underwent angiography within three hours of treatment. In patients with VF the mean (SD) time to peak CK was 24·3 (3·1) hours (range 19–29 hours). The time to peak activity of the CK-MB isoenzyme was similar (23·0 (2·7) hours), showing that cardioversion had not significantly altered the time course of enzyme release. In patients in whom the reperfusion state was angiographically defined the mean time to peak CK was 10·8 (2·9) hours (17 patients, range 6–15 hours) in those with a patent infarct related vessel, compared with 24·0 (5·1) hours (10 patients, range 16–31 hours) in those with persistent occlusion. The enzyme release profile in patients with VF therefore corresponded closely with that in patients with angiographically proven persistent occlusion.

Our results suggest that reperfusion is not a common cause of VF in AMI. As a corollary, the majority of patients with VF complicating AMI have not reperfused and may benefit from thrombolytic treatment.

Coronary atheroma evolution: patterns, correlates, and clinical implications

M B Buchalter, P J Quigley, M J Walsh, B J Maurer, G F Gearty
Royal City of Dublin Hospital, Dublin, Ireland

We reviewed 77 patients who had had coronary angiography on two occasions. The mean interval between the studies was 21·6 months. Between the two studies there was a deterioration of symptoms in 55 patients (71%) and infarction in 15 (19%); while in 18 (23%) the symptoms were unchanged. Of the 274 lesions studied, progression was seen in 97 (35%), no progression in 144 (53%), and regression in 33 (12%). We identified 69 new lesions on the second study. No particular artery was susceptible to progression but lesions progressed more often in the mid segments than the proximal segments of vessels ($p<0\ 05$). New lesions occurred uniformly throughout all segments of all vessels. A change in the mode of treatment was suggested in 43% of patients after the second study and 45% of those who were originally suitable for operation were either unsuitable or required a different graft pattern. In both these groups the interval between studies was longer than in the groups in which treatment was unchanged ($p<0\ 05$). No significant correlation was seen between overall progression, defined as an increase in the Gensini score, and either interval or the risk factors smoking, hypertension, hyperlipidaemia, or family history of ischaemic heart disease.

Coronary atheroma evolves erratically and unpredictably without correlation with known risk factors. Clinical decisions need to be changed more often as the time from the initial study increases.

The value of exercise testing and thallium scintigraphy in identifying patients with myocardial ischaemia after thrombolytic treatment

R S Hornung, K J Hogg, F G Dunn, W S Hillis
Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow

Patients who have undergone successful thrombolysis often have a severe residual stenosis of the infarct related artery. This may lead to ischaemia in the region of the infarct or further infarction if the vessel reoccludes. In order to identify these patients who may then require angioplasty or coronary artery surgery, we performed exercise testing and thallium scintigraphy in 58 subjects at a mean interval of 11·6 weeks after acute myocardial infarction which had been treated successfully by thrombolytic treatment. Coronary artery patency was confirmed angiographically and all patients had a severe residual stenosis (> 75%) of the infarct related vessel. Eleven (19%) patients had a positive exercise test. Twelve (20%) patients were found to have a "reversible" thallium perfusion deficit in the regions supplied by the infarct related vessel (six patients had both a positive exercise test and a reversible thallium perfusion deficit). Forty (69%) patients had a "fixed" perfusion deficit and the remaining six patients had no perfusion deficit (all inferior infarcts). There was no significant difference in the interval from the onset of symptoms of myocardial infarction to the administration of thrombolytic treatment between the reversible and fixed perfusion deficit groups (3 2 and 2·9 hours respectively). At the time of study six of the 12 patients with reversible thallium deficits had developed exertional angina and 12 of the 40 patients with fixed deficits had become symptomatic (correlation, NS); one patient in each group had confirmed reinfarction.

We conclude that exercise testing and thallium scintigraphy are of limited value in detecting residual myocardial ischaemia after thrombolytic treatment even in those patients with continuing symptoms.

Sectional Fourier analysis of gated cardiac tomograms

M Y Norton, S Walton, N T S F Evans
Aberdeen Royal Infirmary, Aberdeen

A technique is described for the production and analysis of ECG gated tomograms of the left ventricle. Tomographic slices were produced with a multidetector emission tomographic scanner, after in vivo erythrocyte labelling with technetium-99m. ECG gated data were recorded in list mode and later used to construct a series of tomograms, which can be displayed in any projection as an endless loop movie for visual inspection. Further analysis involved the derivation of a series of short axis sections at right angles to the long axis of the left ventricle. Each was split into four segments and the amplitude, phase, and ejection fraction of each segment were calculated. For each segment and for each variable, a "normal" range was constructed from the data from 11 subjects with normal wall motion at cardiac catheterisation. The values of 13 subjects with abnormal wall motion at catheterisation were tested against this normal distribution. Abnormal values only were displayed on a bulls-eye representation of the ventricle. There was complete separation of normal and abnormal subjects. Furthermore, the sectional analysis provided an accurate reflection of the site and severity of the wall motion abnormality.

Sex differences in the left ventricular response to exercise in patients with syndrome X

J L Caplin, L Favaro, J J Fettiche, D S Dymond
St Bartholomew's Hospital, London

Syndrome X, chest pain with evidence of ischaemia in patients with normal coronary arteries, remains a therapeutic and diagnostic challenge. Early reports suggested a female preponderance, but new evidence shows an equal sex incidence. To access whether there are any differences between the sexes in the response of the left ventricle to exercise we used first pass radionuclide angiography to study 32 patients (18 men, 14 women) with syndrome X. There were no significant differences between men and women in age, symptoms, or electrocardiographic abnormalities. Resting heart rate was significantly higher in women than men ($p < 0{\cdot}05$), but exercise heart rate was not significantly different. Exercise duration in men was 6·6 (2·1) min and in women it was 4·1 (1·5) min ($p < 0\ 01$). Resting left ventricular ejection fraction was not significantly different (63 (10%) in men and 63 (9%) women), but on exercise there was a significant fall in women to 54 (10%) ($p < 0{\cdot}01$ *vs* rest), but not in men (to 60 (15%), p not significant *vs* rest). Exercise left ventricular function was abnormal in seven men and 10 women and regional function was abnormal in four men and eight women. Only exercise duration had any significant linear correlation with left ventricular exercise response, but this was weak ($r = 0{\cdot}41$, $p < 0{\cdot}05$).

Abnormalities in exercise left ventricular function in a group of patients with syndrome X occur mainly in women and may reflect a difference in aetiology between the sexes. These differences suggest that the sex of the patient is important in the interpretation of non-invasive information in suspected coronary artery disease.

Failure of coronary anatomy to predict accurately left ventricular dysfunction on exercise

J L Caplin, L Favaro, J J Fettiche, D S Dymond
St Bartholomew's Hospital, London

To investigate the variable relation between the extent of coronary disease and the resultant left ventricular dysfunction on exercise, the results of first pass radionuclide angiography were reviewed in 135 patients with angiographic coronary disease and preserved left ventricular function. Fifty-one patients had one vessel disease, 37 had two vessel disease, and 47 had three vessel disease. Resting left ventricular ejection fraction was greater in one vessel disease (59 (8%) mean (SD)) than in two vessel disease (55 (9%), $p < 0{\cdot}05$), or in three vessel disease (54 (9%), $p < 0{\cdot}01$). Exercise left ventricular ejection fraction fell significantly in each group ($p < 0{\cdot}001$) but the fall was less in one vessel disease (to 50 (9)%) than in three vessel disease (41 (12)%) ($p < 0{\cdot}001$). There were no significant differences in exercise haemodynamic function, exercise duration, or change in left ventricular ejection fraction with exercise. Two additional indices that related change in left ventricular function to exercise duration and to heart rate slope were derived, but although there were some significant differences between the groups, the extent of overlap precluded accurate prediction. Multiple stepwise regression analysis showed exercise left ventricular ejection fraction to be the best and only independent predictor of coronary anatomy ($r = 0{\cdot}35$, $p < 0{\cdot}001$), but with a high degree of scatter.

There appears to be some relation between the extent of coronary obstruction and left ventricular dysfunction on exercise; however, a simple anatomical classification fails to predict accurately the extent of functional impairment. This suggests that studies of the effect of interventions in coronary disease should include a functional as well as an anatomical classification.

Floppy mitral and aortic valves: a common combination

Jacqueline Morton, Christine Rodger
Monklands District General Hospital, Airdrie

Over a 28 month period a classically floppy mitral valve was diagnosed in 117 new patients referred for echocardiography. Of these patients 50 had a normal aortic valve, 48 had echocardiographic features of a floppy aortic valve, and we identified intermediate features in 19. Doppler ultrasound (85 patients) showed no significant systolic gradients across any of the aortic valves: the frequency of aortic regurgitation in the 42 floppy, 32 normal, and 11 intermediate valves studied was 64·3%, 9·4%, and 0, respectively.

In patients with floppy mitral valves additional myxomatous degeneration of the aortic valve is common and such valves are often mildly regurgitant.

Signal averaged ECG and Doppler aortic blood flow after myocardial infarction

T Cripps, Susan Gilmore, D Mannering, D Bennett, J Camm, D Ward
Department of Cardiological Sciences, St George's Hospital, London

Transcutaneous continuous wave Doppler aortic blood flow and the signal averaged ECG were studied in 74 consecutive patients admitted after acute myocardial infarction (MI). Patients also had radionuclide or angiographic assessment of left ventricular function and 24 hour ECG. Patients with bundle branch block (5), atrial fibrillation (1), and complete heart block (1) were excluded from the signal averaged ECG analysis. A positive result (one or more of: filtered QRS > 120 ms, terminal QRS duration below 40 µV for > 40 ms, and RMS voltage during last 40 ms of < 25 µV) was present in 15/67 patients (22%). An abnormal signal averaged ECG was found more often in those with non-Q MI (8/23(35%) non-Q *vs* 7/39(18%) Q, $p<0{\cdot}05$). Peak enzyme activities were higher in those with an abnormal signal averaged ECG (aspartate transaminase 242 (35) *vs* 174 (13) IU/l and 2-hydroxybutyrate dehydrogenase 738 (47) *vs* 556 (36) IU/l, $p<0{\cdot}0001$). Doppler studies showed a significant correlation between maximum acceleration and the angiographic and radionuclide ejection fractions ($p<0{\cdot}001$, $r = 0{\cdot}75$). The maximum acceleration was lower in patients with an abnormal signal averaged ECG (11 (3) *vs* 16 (4) $\mathrm{ms}^{-1}\,\mathrm{s}^{-1}$, $p<0{\cdot}001$). There was no correlation between the results of ambulatory ECG monitoring and the signal averaged ECG. During follow up, seven (10%) patients died; in one death was thought to be caused by pulmonary oedema and rapid atrial fibrillation and in another to reinfarction. Of the remaining five patients, who suffered deaths from arrhythmia, the signal averaged ECG was abnormal in four; 11 of the 67 survivors had an abnormal signal averaged ECG.

We conclude that: (*a*) transcutaneous Doppler is a useful indicator of left ventricular function and MI; (*b*) an abnormal signal averaged ECG is more common in patients with impaired left ventricular function after MI; (*c*) both techniques merit further study in this context because they are non-invasive, inexpensive, and easily performed, and they provide useful information which may enhance risk stratification in patients after myocardial infarction.

A quart into a pint pot: computer modelling to improve cardiac surgical throughput

R C Parry, C Ratnatunga, T Treasure
Coppers and Lybrand Associates and The Middlesex Hospital, London

We have written a computer program to model the activity of a cardiac surgical unit. The number of operating sessions and beds, whether in intensive therapy unit (ITU) or wards, are defined constraints, and the user specifies a representative spectrum of patients to provide a data base from which the computer by simulation, admits, operates, and discharges cases. Throughput and bed occupancy figures are provided for each area of practice. Our unit has 16 beds, four days operating, and unpredictable use of 2–4 ITU beds. Day case work-up and early district hospital transfer were included in the model. The computer simulation achieved 310 cases with 92% bed occupancy and relative under usage of theatre (72%) and ITU (62%). In 1985 over 400 bypass cases, and additional closed operations, were performed, with ostensibly, the same constraints. In practice flexible management strategies were used to achieve the 90 extra cases. By using the model we explored the impact of admission of predictable postoperative problem cases late in the week and other selective admission policies, transfer of long stay cases (> 4 days) to general ITU beds, and the recognition of extra operating, arbitrarily timed on Saturday. When these were incorporated in the model, 410 cases were achieved.

Dipyridamole versus exercise thallium imaging: comparable or not?

J P Bourke, T Hawkins
Freeman Hospital, Newcastle upon Tyne

Although exercise is the conventional method of obtaining myocardial stress during thallium imaging, intravenous dipyridamole (DP) now provides an alternative and extends stress imaging to patients who exercise poorly. The two techniques are mechanistically different, however. A study was performed to compare the quality of the stress images obtained by both techniques to define better the role of DP stress imaging.

Exercise was performed according to a limited Bruce protocol test and DP was given by an intravenous infusion (0·5 mg/kg over 4 minutes). Thallium-201 (75 MBq) was injected 60 s before the completion of treadmill exercise and in the DP group after gentle walking on the spot exercise. Images were obtained in the left anterior oblique (LAO), left lateral, and anterior views with a gamma camera and associated computer system. An image quality index was derived from the ratio of the maximum myocardial uptake segment to uptake in a fixed lung segment. The LAO view was used. Normalised thallium counts for both myocardium and lung were also compared.

The images of 30 consecutive DP and 30 exercise studies in the same time period were studied. The mean exercise duration in the exercise group was 7·33 minutes (range 3–12 66). The mean myocardial uptake of thallium was significantly higher in the DP group (140 (45) *vs* 101 (29) counts/s/unit area; $p < 0\ 001$); however, the lung-background uptake was also higher (69 (22) *vs* 47 (10) counts/s/unit area; $p < 0\ 001$). As a consequence the indices of image quality were not significantly different (2·06 (0 29) *vs* 2·14 (0·36); $p > 0{\cdot}1$).

DP and exercise stress give similar quality thallium images. These technical data support the more widespread use of the DP stress technique.

Improved functional capacity in patients with hypertrophic cardiomyopathy treated by dual chamber pacing

K McDonald, E McWilliams, B J Maurer, D B O'Keeffe
St Vincent's Hospital, Dublin, Ireland and City Hospital, Belfast, Northern Ireland

Work already presented to the British Cardiac Society has documented improvement of haemodynamic function and symptoms in patients with hypertrophic cardiomyopathy treated with dual chamber pacing (DDD). The present cooperative study was designed to compare functional capacity, as assessed by sequential exercise testing, in paced and in sinus rhythm. Fourteen patients have been entered in this study. Eleven patients have been followed for at least one year and the results of eighteen pairs of exercise tests on these patients are presented. In seven patients in whom repeated exercise tests were carried out, the order of testing was reversed on the second occasion. In all cases exercise was symptom limited and terminated by dyspnoea or fatigue or both. Mean (SD) treadmill endurance time was increased from 7·23 (3·37) minutes to 9·74 (3·86) ($p = 0{\cdot}0012$). All eleven patients improved by at least one functional class as assessed by Canadian Heart Association criteria. Before pacing nine were in class 3 or 4 and 2 were in class 2. One year after pacing seven were in class 2 and 4 in class 1.

These observations demonstrate a significant and sustained improvement in exercise tolerance, and support the previously reported haemodynamic and subjective improvement in patients with severely symptomatic hypertrophic cardiomyopathy treated with dual chamber pacing.

Inappropriate use of intravenous verapamil in patients with ventricular tachycardia

A C Rankin, A P Rae, S M Cobbe
Department of Medical Cardiology, Royal Infirmary, Glasgow

Intravenous verapamil is an effective treatment for supraventricular tachycardia (SVT) but it has also been used for broad complex tachycardia, where the diagnosis is uncertain. The response to intravenous verapamil in 29 episodes of ventricular tachycardia (VT), incorrectly diagnosed as SVT, was analysed. There were 17 patients (13 men, 4 women) aged 35–85 years (mean 59 years). Underlying heart disease was present in 15 patients: coronary artery disease in 12 and cardiomyopathy in three. The mean tachycardia rate was 190 (25) beats/min (range 150–240 beats/min). The mean QRS duration was 0·15 (0·01) s. Electrocardiographic features consistent with VT were present in all patients, and the diagnosis was confirmed by electrophysiological study in 12. Verapamil was administered in dosages ranging from 2·5 mg to 30 mg (mean 11·2 (6·1) mg). In 23 episodes (79%) the tachycardia was not terminated, and in 13 of these severe hypotension occurred. Cardiac arrest occurred in two patients (caused by asystole in one and ventricular fibrillation in the other). The mean systolic blood pressure of those in whom the tachycardia persisted was 100 (22) mm Hg before and 83 (17) mm Hg after verapamil ($p < 0{\cdot}01$). In 16 episodes DC cardioversion was required to terminate the tachycardia. No serious haemodynamic effects were observed in 12 episodes. In two patients without underlying heart disease, sinus rhythm was restored in four episodes. At least one serious adverse effect occurred in 10 patients (59%).

Verapamil is ineffective and potentially hazardous in VT and its use is inappropriate for the treatment of broad complex tachycardia unless a supraventricular origin has been clearly established.

Wolff-Parkinson-White syndrome: rapid ventricular response to atrial fibrillation in previously asymptomatic individuals

K Robinson, E Rowland, D M Krikler
Royal Postgraduate Medical School, Hammersmith Hospital, London

Atrial fibrillation (AF) is a potentially lethal complication of the Wolff-Parkinson-White (WPW) syndrome; reentrant atrioventricular tachycardia (RAVT) is considered to be an important mechanism in precipitating it. Furthermore, when AF complicates WPW syndrome there is usually a history of prior symptomatic RAVT. We analysed the clinical presentation, electrocardiograms, and electrophysiological data of 108 consecutive symptomatic patients with the WPW syndrome. In nine (8%) AF was documented as the arrhythmia at the time of their first episode of palpitation. One presented with atrial flutter with 1:1 conduction. There were four women and six men. Though the mean age was 40 years, a bimodal age distribution was noted; four were 24 years or younger and six were 47 years or older. All complained of palpitation: three were presyncopal and three had syncope. Three had angina at presentation and one was hypertensive. Seven had type A WPW and three had type B. The range of mean ventricular rates observed clinically during AF was 125–259/min, whereas at electrophysiological study it was 173–310/min. The range of anterograde effective refractory periods of the accessory bundle was 230–290 ms.

AF may occur in the absence of antecedent RAVT, and dangerously high ventricular rates may be the first symptomatic manifestation of the WPW syndrome. The absence of a history or RAVT does not exclude the possibility of lethal arrhythmias. However, the role of prospective electrophysiology testing in symptom free patients, in whom the risk of sudden death appears to be minimal, remains to be established.

Intracavitary flow patterns in hypertrophic cardiomyopathy: a pulsed and continuous wave Doppler study with colour flow mapping

P Nihoyannopoulos, Y Yonezawa, W J McKenna, Celia M Oakley

Hammersmith Hospital, Royal Postgraduate Medical School, London

Previous work has shown a direct relation between the extent of systolic anterior motion of the mitral valve (SAM) and measured intracavitary gradients in hypertrophic cardiomyopathy (HCM). We have now studied intracavitary left ventricular (LV) systolic flow patterns and velocity profiles in 47 consecutive patients with HCM using combined colour flow mapping with continuous and pulsed wave Doppler. Sixteen patients had complete SAM of the mitral valve, 14 had incomplete SAM, and 17 patients had no SAM. These were compared with the flow velocity patterns obtained from 10 normal individuals. All patients were in sinus rhythm. In normal individuals and patients without SAM colour flow mapping revealed laminar flow throughout systole with peak velocities of 0·65 (0·12) and 1·1 (0·2) m/s respectively ($p < 0{\cdot}05$). In patients with incomplete and complete SAM there was laminar flow until the onset of SAM (106 (22) ms) when aliasing with colour reversal was seen at papillary muscle level; peak velocity at this level was 1·4 (0·5) m/s. After the onset of SAM septal contact (232 (37) all patients with complete SAM had a green-mosaic pattern of turbulent flow in association with an increase of peak velocity to 3·8 (1·1) ms.

Since the peak velocities were increased but similar in all patients before the onset of SAM, SAM cannot have been initiated by a Venturi effect as has been suggested, but such an effect could have been responsible for its later maintenance.

Br Heart J 1987;57:593

Correspondence

Influence of profuse sweating on systolic time intervals

Sir,
We compliment Ishikawa and Ishikawa (1986;56: 176–8) on their interesting data, but we have some reservations about their conclusions and interpretation of the haemodynamic mechanisms.

They clearly define the influence of a sauna (and presumably profuse sweating) on systolic time intervals as producing a prolonged pre-ejection period and pre-ejection period divided by ejection time, a shortened ejection time, and an unchanged electromechanical systole. Heart rate and blood pressure were unchanged and haematocrit and body weight decreased. Ishikawa and Ishikawa conclude "...systolic time intervals measured after profuse sweating can give a false impression of cardiac function". In contrast, we believe that they gave a true impression and that cardiac function really was reduced after sweating.

A prolonged pre-ejection period, especially with a shortened ejection time, is an acknowledged hallmark of reduced cardiac performance (by any mechanism). Heart rate was unchanged and, therefore, was not contributory. Since blood pressure was unchanged, afterload probably was stable. Although Ishikawa and Ishikawa did not investigate preload (for example by echocardiography), the acute decreases in haematocrit and body weight indicate reduced blood volume consistent with preload reduction. Indeed, the changes in systolic time intervals are identical with those seen after preload reduction[1 2] and can be explained by a leftward shift of the Frank-Starling curve. Finally, electromechanical systole (QII_c), which is very sensitive to changes in contractility,[3 4] was stable.

Thus we conclude that cardiac function was indeed altered by the sauna and that this was probably the result of preload reduction rather than reduced contractility. We recommend that load-dependent measurements, such as the pre-ejection period and its ratio to ejection time, are best interpreted after taking into account simultaneously measured information about loading conditions.

Gustav G Belz,
Institute for Cardiovascular Therapy,
Alwinenstrasse 16,
6200 Wiesbaden,
Federal Republic of Germany.

David H Spodick,
Division of Cardiology,
St Vincent Hospital,
University of Massachusetts,
Worcester, MA 01604,
USA.

References

1 Buch J, Egeblad H, Hansen PB, Kjaergård H, Waldorff S, Steiness E. Correlation between changes in systolic time intervals and left ventricular end-diastolic diameter after preload reduction. Non-invasive monitoring of pharmacological intervention. *Br Heart J* 1980;44:668–71.
2 De La Paz LR, Kerigan AT, Koch GG, Kolman WA, Spodick DH. Erythrityl tetranitrate: changes consistent with sustained preload reduction. *Am J Med Sci* 1979;277.173–8
3 Lewis RP, Rittgers SE, Forester WF, Boudoulas H A critical review of the systolic time intervals *Circulation* 1977;56:146–58.
4 Stern HC, Matthews JH, Belz GG. Influence of dihydralazine induced afterload reduction on systolic time intervals and echocardiography in healthy subjects. *Br Heart J* 1984;52:435–9.

Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

The Annual General Meeting for 1988 will take place in Belfast on 23 and 24 March 1988, and the closing date for receipt of abstracts will be 4 January 1988.

Cardiac Society of Australia and New Zealand

The 35th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand will be held in Melbourne on 2 to 5 August 1987. Inquiries to: Mr K J Wickham, PO Box 235, North Balwyn 3104, Australia.

Health education

The XIII World Conference on Health Education will be held in Houston on 28 August to 2 September 1988. For further information write to the US Host Committee, PO Box 20186, Suite 902, Houston, Texas 77225, USA.

Correction

Editorial: Twenty years of prehospital coronary care *J S Geddes*—we apologise for an error in the December 1986 issue (volume 56: page 491, right hand column, second paragraph, lines 3 and 4) where "hospital morbidity was only 9%" should read "hospital mortality was only 9%".

Br Heart J 1987;57:595–6

List of advisers

We thank the following who have reviewed manuscripts submitted to the British Heart Journal during 1986.

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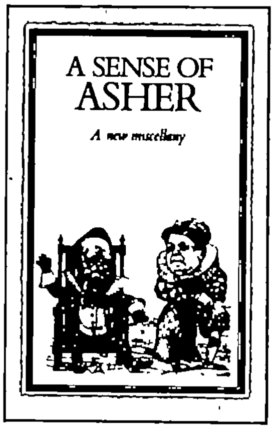

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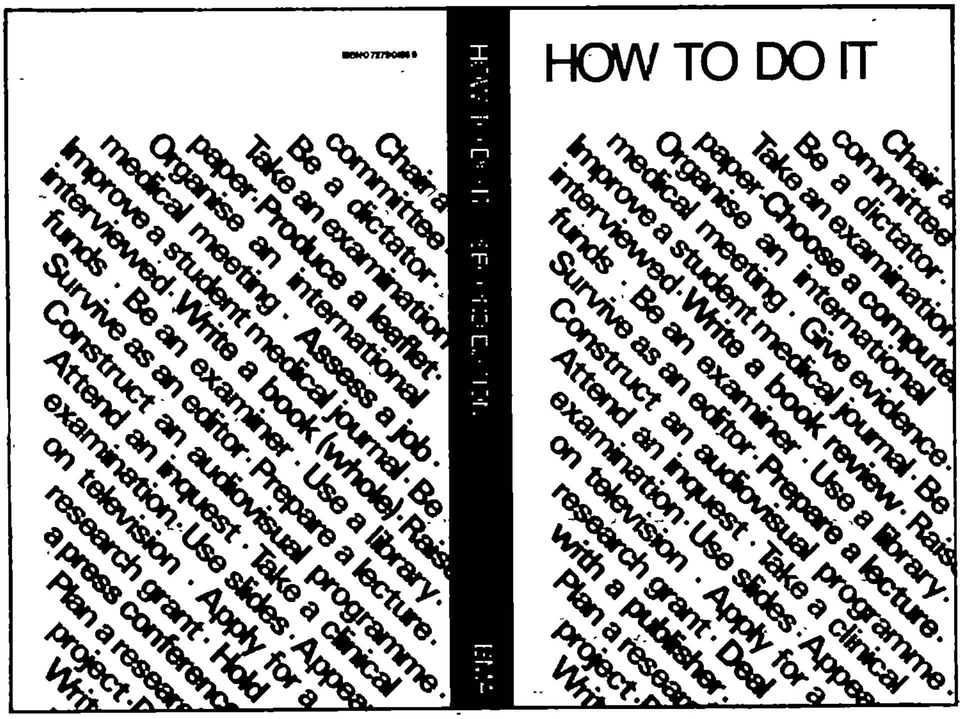
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Candidates who should hold a Diploma of Fellowship of a Surgical College or an equivalent Diploma are required to have three years' post-Fellowship experience in Cardiothoracic Surgery of which one year must have been completed in an approved centre in the United Kingdom. Candidates must submit written evidence of their experience in the specialty including their operative experience.

The application form, examination calendar and Regulations are available on request from the Examinations Secretary, The Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW.

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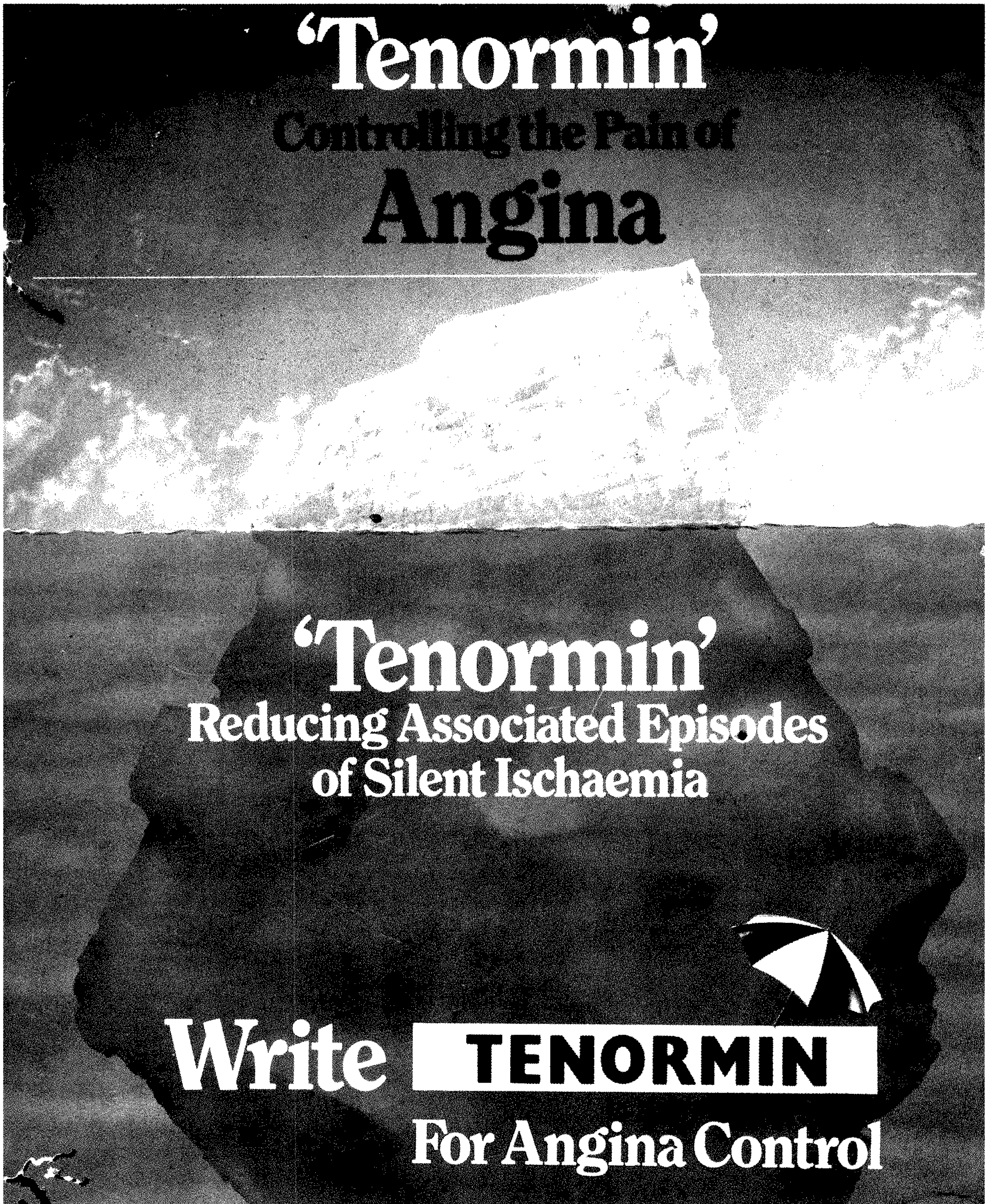

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